

Contemporary Endocrinology

Series Editor: Leonid Poretsky

Rifka C. Schulman-Rosenbaum *Editor*

Diabetes Management in Hospitalized Patients

A Comprehensive Clinical Guide



Springer

Contemporary Endocrinology

Series Editor

Leonid Poretsky, Division of Endocrinology

Lenox Hill Hospital

New York, NY, USA

Contemporary Endocrinology offers an array of titles covering clinical as well as bench research topics of interest to practicing endocrinologists and researchers. Topics include obesity management, androgen excess disorders, stem cells in endocrinology, evidence-based endocrinology, diabetes, genomics and endocrinology, as well as others. Series Editor Leonid Poretsky, MD, is Chief of the Division of Endocrinology and Associate Chairman for Research at Lenox Hill Hospital, and Professor of Medicine at Hofstra North Shore-LIJ School of Medicine.

Rifka C. Schulman-Rosenbaum
Editor

Diabetes Management in Hospitalized Patients

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To my husband (and best friend) Avi, for the endless love, support, and encouragement, and for handling parent duty for all the countless hours of weekend time devoted to this book. Thank you, I could not have done this without you!

To my children Rachel, Moshe, and Gabby, for cheering me on and for sharing me with medicine, this book and other endeavors.

Rachel—Thank you for twenty years (and counting) of proud mama moments, looking forward to seeing great things from you, my “sister”. Moshe—Your easy going personality is truly appreciated, now time for a screen break. Gabby—You are the family treasure, and future endocrinologist, class of 2044.

Foreword

Diabetes mellitus is arguably the most common diagnosis encountered in hospitalized patients. Although relatively few patients are hospitalized with a primary diagnosis of diabetes, many patients on both medical and surgical services have diabetes as a complicated condition. Admission and readmission rates are significantly increased for patients with diabetes and appropriate management of diabetes in hospitalized patients can improve outcomes and reduce the length of stay.

Dr. Rifka C. Schulman-Rosenbaum has assembled an impressive group of experts to address all aspects of diabetes in hospitalized patients. The topics include diabetes management when diabetes is a primary or a secondary diagnosis (for the latter group including a primary diagnosis of COVID-19), nutritional aspects in hospitalized patients with diabetes, perioperative management, diabetes in patients with oncological diagnoses, and multiple other topics spanning 30 chapters. A thorough discussion of diabetes technology as it relates to the hospital setting is also included.

This monograph without a doubt will be an extremely useful source of information for physicians in multiple specialties as well as students of medicine at all levels. The editor and the contributors can be proud of their remarkable accomplishment.

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Leonid Poretsky,

Preface

Diabetes mellitus has become increasingly prevalent in the United States and worldwide. In conjunction with the epidemic of obesity, the sheer numbers of patients with diagnosed and undiagnosed type 2 diabetes are straining the healthcare system, including a high prevalence of diabetes patients in the hospital setting. Frequently 25–30% of hospital patients have diabetes, with concomitant hyperglycemia and hypoglycemia which impacts morbidity and mortality.

Inpatient diabetes management has become increasingly more complex following the advent of many newer pharmacotherapy options as well as devices including insulin pumps and continuous glucose monitors. Patients often have other comorbidities such as renal impairment or cancer, or require specialized surgery or nutritional approaches, all with important differences when it comes to diabetes care. Furthermore, differentiating the unique types of diabetes mellitus that may be encountered in the inpatient setting is critical, as management differs in some key areas. Because of the high prevalence of diabetes in the hospital, having the ability to properly care for patients requires not only skilled endocrinologists and endocrine fellows but the close involvement of internal medicine hospitalists and other specialty physicians (i.e., emergency department, surgery, obstetrics, critical care), residents, medical students, nurse practitioners, physician assistants, pharmacists, nurses including Certified Diabetes Care and Education Specialists, registered dietitians, and more. Diabetes is encountered in all segments of the hospital; its effects are far reaching. Improving inpatient diabetes management can affect healthcare cost and benefit the hospital both financially and from a quality management standpoint. Discharge planning and diabetes education are also fundamental components of management to ensure a safe transition from inpatient to the outpatient setting and to prevent readmissions.

This book is designed to provide practical guidance on diabetes management for hospitalized patients. The number of topics covered is meant to be comprehensive and include discussion on many potential scenarios encountered on the inpatient service, but in a concise and user-friendly manner. I hope that it will be extremely

useful for both learners (fellows, residents, students) and existing providers looking to improve their knowledge and skills in evidence-based inpatient diabetes management. Importantly, I am indebted to the incredible panel of authors among the 30 enclosed chapters, including many globally renowned physicians, researchers, and clinicians.

New Hyde Park, NY, USA

Rifka C. Schulman-Rosenbaum

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- Dr. Yael Tobi Harris for the idea of editing a book and the ongoing and much appreciated support.
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- Dr. Tracy Breen for hiring me as an inpatient endocrinologist after fellowship and being an inspiring and accomplished female role model.
- My inpatient diabetes team at Long Island Jewish Medical Center for tackling the daily challenges of diabetes care and the pursuit of excellence.
- To 12 years of endocrine fellows, I have rounded with day in and day out and provided opportunities of mutual ongoing education.
- To my loving parents for cheering me on since childhood and still putting my work on the refrigerator.
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Part I

Basics of Inpatient Diabetes Management

Chapter 1

The History of Inpatient Diabetes



Danielle Brooks, Rifka C. Schulman-Rosenbaum, Rodolfo Galindo,
and Guillermo E. Umpierrez

Introduction

Within the timeline of modern medicine, the history of diabetes treatment is comparatively brief, yet monumental. After the discovery of insulin by Banting and Best in 1921, the first successful use of insulin occurred in a 14-year-old patient with diabetic ketoacidosis in 1922. It was not until 1936 that the first modified insulin using animal products derived from cattle and pigs was introduced. The first synthetic, genetically engineered insulin using *E. coli* was introduced in 1978, while synthetic analog insulins became available in the 1980s, and the newest analogs were introduced in the last 20 years [1–3]. Randomized

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controlled trials involving insulin use for diabetes management in the hospital have occurred more recently in the history of medicine. In this chapter, we review the history of inpatient diabetes management as it pertains to the landmark trials, clinical practice guidelines, and evolving models of diabetes care in the hospital setting.

Inpatient Diabetes Epidemiology

The prevalence of diabetes mellitus is rising. As of 2022, 11.3% of Americans have diabetes [4]. Of those with diabetes, approximately 77% have a known diagnosis, whereas the remaining cases are undiagnosed. There are 1.4 million new diabetes diagnoses each year [4]. The number of diabetes-related hospitalizations per year has increased significantly since 2000, nearly doubling to greater than 8.2 million hospitalizations in 2018 [5]. The total costs of diabetes care in the United States have matched this rising prevalence, increasing by 26% from 2012 to 2017, to \$327 billion annually [6]. Inpatient diabetes accounts for approximately 30% of total costs of diabetes care [6].

Hyperglycemic emergencies are frequently encountered in inpatient medicine. A 2015 observational study revealed that approximately 23% of intensive care unit (ICU) admissions involve patients with diabetes mellitus with 9.3% of patients having had undiagnosed diabetes prior to their hospitalization [7]. Data from 2009 to 2014 shows that the age-adjusted rate of diabetic ketoacidosis (DKA)-related hospitalizations increased by 54.9% to 30.2 per 1000 persons, with an average annual rate of increase at 6.3%; fortunately, inpatient DKA-related mortality rates in the United States have declined over time [8]. In 2018, the rate of DKA-related hospitalizations was more frequent than that of hyperglycemic hyperosmolar syndrome (HHS) [9].

It is well established that hyperglycemia is associated with adverse outcomes including increased hospital mortality and prolonged hospitalizations in patients with and without diabetes [10–13]. Inpatient hyperglycemia management has changed over time to optimize patient care to treat the growing diabetes population and avoid the negative consequences of both hyperglycemia and hypoglycemia [14, 15]. Here, we will review the landmark studies that have served as the foundation of modern-day inpatient diabetes practice. A timeline of these studies is illustrated in Fig. 1.1, and summary of their key findings can be found in Table 1.1 for the critically ill population and Table 1.2 for the non-critically ill population.

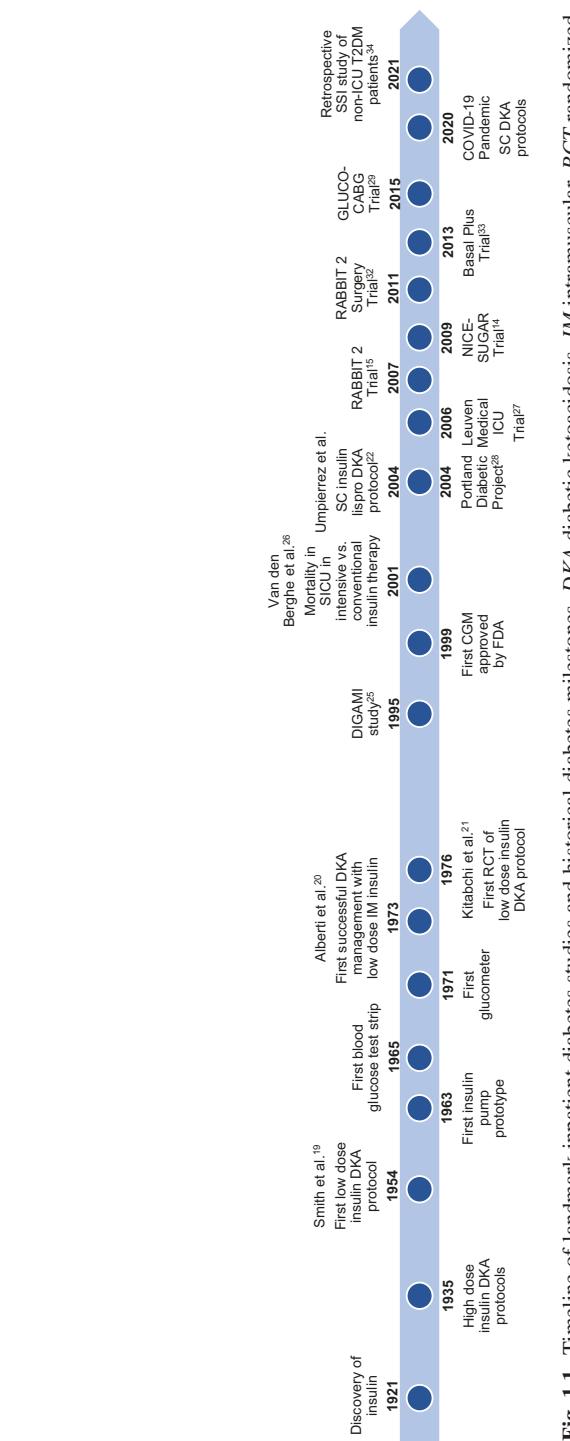


Fig. 1.1 Timeline of landmark inpatient diabetes studies and historical diabetes milestones. *DKA* diabetic ketoacidosis, *IM* intramuscular, *RCT* randomized controlled trial, *CGM* continuous glucose monitor, *FDA* U.S. Food and Drug Administration, *SICU* surgical intensive care unit, *SC* subcutaneous, *SSI* sliding-scale insulin, *T2DM* type 2 diabetes mellitus

Table 1.1 Summary of landmark inpatient diabetes studies in critically ill patients (ICU)

| First author (year) | Study design | Study population | Primary objective | Intervention | Key findings |
|----------------------|---------------|--------------------------|---|---|---|
| Alberti (1973) [16] | Observational | $N = 14$ DKA patients | To describe a new regimen for diabetic coma using low-dose IM regular insulin | <i>Low-dose protocol:</i> initial mean insulin dose: 16 ± 2 units, then 5–10 units IV or IM hourly | Low-dose IM insulin is effective in DKA treatment |
| Kitabchi (1976) [17] | RCT | $N = 48$ DKA patients | To compare low-dose IM insulin to high-dose IV and SC insulin in DKA | <i>High-dose protocol:</i> ≥ 10 units IV insulin + 30 units of SC insulin (if BG 300–399 mg/dL), increased up to IV 50 units with 100 units SC (if BG ≥ 1000 mg/dL). Both groups were followed by 50 units/h of SC insulin <i>Low-dose protocol:</i> 0.1 unit/lb body weight IM insulin followed by 5 units/h IM insulin | Less insulin was needed to correct BG to <250 mg/dL in the low-dose group (46 ± 5 units vs. 263 ± 45 units, $P <0.001$)*** No patients in the low-dose group experienced hypoglycemia. 25% in the high-dose group developed hypoglycemia The rate of DKA resolution was similar between the groups |

Table 1.1 (continued)

| First author (year) | Study design | Study population | Primary objective | Intervention | Key findings |
|-------------------------------------|--------------|---|---|--|---|
| Malmberg (DIGAMI study) (1995) [18] | RCT | $N = 620$ Hyperglycemic patients with acute myocardial infarctions in 19 Swedish CCUs Hyperglycemia was defined as >198 mg/dL | To assess the impact of an insulin-glucose infusion protocol on mortality in patients with diabetes at 1 year following myocardial infarction | <i>Insulin-glucose infusion protocol:</i> 500 mL 5% glucose with 80 IU insulin, initiated at 30 mL/h. Infusion was adjusted per a nurse-guided protocol to target BG 126–196 mg/dL, followed by multidose SC insulin for at least 3 months <i>Conventional group:</i> insulin given according to standard of care | The insulin-glucose infusion intervention improved outcomes in patients with diabetes who experienced myocardial infarctions In-hospital morbidity was similar between the groups (i.e., reinfarction, arrhythmias, congestive heart failure) At 3-month follow-up, the insulin-glucose infusion group had better glycemic control (HbA1c $7 \pm 1.6\%$ vs. $7.5 \pm 1.8\%$, $P < 0.01$)*** The overall 1-year mortality was lower in the insulin-glucose infusion group (18.6% vs. 26.1%, $P = 0.0273$)*** |

(continued)

Table 1.1 (continued)

| First author (year) | Study design | Study population | Primary objective | Intervention | Key findings |
|----------------------------|--------------|---|---|---|---|
| Van den Berghe (2001) [19] | RCT | $N = 1548$ Mechanically vented SICU patients | To assess mortality and morbidity in patients receiving intensive versus conventional insulin therapy in the SICU | <i>Intensive insulin group:</i> BG target 80–110 mg/dL; insulin infusion started if BG >110 mg/dL <i>Conventional therapy:</i> BG target 180–200 mg/dL; insulin infusion only if BG >215 mg/dL When the patient was discharged from the ICU, BG was maintained at 180–200 mg/dL for both groups | ICU mortality was lower in the intensive group (4.6% vs. 8%; $P < 0.04$)*** with a mortality risk reduction of 42% (95% CI, 22–62%) In-hospital mortality was also lower in the intensive group, especially due to multiorgan failure with sepsis (8 vs. 33 cases, $P = 0.02$)*** Fewer patients in the intensive group needed prolonged ventilation or renal replacement therapy |
| Umpierrez (2004) [20] | RCT | $N = 40$ DKA patients in general wards, intermediate care units, and ICU | To compare the efficacy of an SC insulin lispro protocol to the standard low-dose IV regular insulin infusion protocol in uncomplicated DKA treatment | <i>SC group:</i> SC insulin lispro 0.3 units/kg and then 0.1 units/kg/h until BG was <250 mg/dL, followed by SC 0.05–0.1 units/kg/h until DKA resolved <i>Infusion group:</i> regular insulin at 0.1 units/kg IV bolus and then the same hourly IV infusion rates as the SC group above until DKA resolved | The rates of hyperglycemia correction and DKA resolution were similar between the groups Hourly SC insulin lispro protocol may be burdensome for general medicine patients |

Table 1.1 (continued)

| First author (year) | Study design | Study population | Primary objective | Intervention | Key findings |
|---|---------------|---|---|---|---|
| Furnary (Portland Diabetic Project) (2004) [21] | Observational | $N = 4864$ Patients with diabetes undergoing cardiac surgery | To describe the in-hospital outcomes of patients with diabetes undergoing cardiac surgery | <i>SC group:</i> $N = 968$, SSI SC injections every 4 h to target BG < 200 mg/dL <i>Insulin infusion group:</i> $N = 3896$, 0.5–1 unit/h (with an IV insulin bolus if glucose was > 240 mg/dL) titrated hourly according to BG using a target of 100–150 mg/dL. The protocol was adjusted to target different BG over the course of the study (i.e., 125–175 mg/dL in 1999–2000, 100–150 mg/dL in 2001–2003) | Perioperative hyperglycemia was associated with increased mortality, wound infections, longer hospitalizations, and increased costs The use of continuous insulin infusion reduced mortality by 57% and wound infection by 66% ($P < 0.0001$)*** |

(continued)

Table 1.1 (continued)

| First author (year) | Study design | Study population | Primary objective | Intervention | Key findings |
|---|--------------|--|--|--|---|
| Van den Berghe (Leuven Medical Trial) (2006) [22] | RCT | $N = 1200$ MICU patients. 16.9% had known diabetes | To compare outcomes in MICU patients receiving intensive insulin therapy versus conventional therapy. Intention-to-treat analysis | <i>Intensive insulin group:</i> insulin infusion if BG >110 mg/dL, BG target 80–110 mg/dL <i>Conventional treatment group:</i> insulin infusion if BG >215 mg/dL with tapering of dose if BG <180 mg/dL | Intensive insulin therapy did not reduce in-hospital mortality (37.3% vs. 40%, $P = 0.33$) The intensive therapy group experienced significantly reduced morbidity compared to the conventional group including less acute kidney injuries, shortened ventilation weaning periods, shorter ICU and hospital stays |
| Finfer (NICE-SUGAR) (2009) [14] | RCT | $N = 6104$ MICU and SICU patients at 42 hospitals | To compare outcomes in ICU patients receiving intensive insulin therapy versus conventional insulin therapy | <i>Intensive insulin group:</i> BG target 81–108 mg/dL <i>Conventional treatment group:</i> BG target ≤ 180 mg/dL; infusion began once BG >180 mg/dL and was stopped once BG <144 mg/dL Both groups received IV insulin infusion | 27.5% of patients in the intensive group died compared to 24.9% in the conventional group (odds ratio for intensive group, 1.14; 95% CI, 1.02–1.28, $P = 0.02$)*** There was no difference between the groups in rates of multiorgan failure, ventilation duration, renal replacement therapy, bacteremia, or blood transfusions Intensive glucose control increased mortality in the ICU. These findings contradict the results published by Van den Berghe et al. (2001) |

Table 1.1 (continued)

| First author (year) | Study design | Study population | Primary objective | Intervention | Key findings |
|------------------------------------|--------------|---|--|---|---|
| Umpierrez (GLUCO-CABG) (2015) [23] | RCT | $N = 302$ Patients with and without diabetes with hyperglycemia after CABG | To compare outcomes in CABG patients receiving intensive insulin therapy versus conventional insulin therapy | <i>Intensive glucose target:</i> BG target 100–140 mg/dL <i>Conservative glucose target:</i> BG target 141–180 mg/dL Both groups used a computer-guided insulin algorithm and received IV insulin. After ICU discharge, patients with diabetes received SC basal or BBI | There were no significant differences between the groups in rates of postoperative infections, respiratory failure, acute kidney injury, or death There were no differences in overall hospital complications in patients with and without diabetes Patients without diabetes in the intensive group experienced less postoperative complications compared to the conservative group (34% vs. 55%, $P = 0.008$)*** |

ICU intensive care unit, *DKA* diabetic ketoacidosis, *IM* intramuscular, *RCT* randomized controlled trial, *IV* intravenous, *BG* blood glucose, *SC* subcutaneous, *CCUs* coronary care units, *HbA1c* hemoglobin A1c, *SICU* surgical intensive care unit, *CI* confidence interval, *SSI* sliding-scale insulin, *MICU* medical ICU, *CABG* coronary artery bypass surgery, *BBI* basal-bolus insulin

***Results were statistically significant

Table 1.2 Summary of landmark inpatient diabetes studies in non-critically ill patients (non-ICU)

| First author (year) | Study design | Study population | Primary objective | Intervention | Key findings |
|--|--------------|---|--|--|--|
| Umpierrez (RABBIT 2) (2007) [15] | RCT | $N = 130$ Nonsurgical insulin-naïve patients with T2DM admitted to general medicine | To compare glycemic control between BBI and SSI in patients with T2DM | <i>BBI</i> : insulins glargin and glulisine using TDD = 0.4–0.5 units/kg adjusted to target BG ≤ 140 mg/dL <i>SSI</i> : regular insulin four times daily for BG > 140 mg/dL. If mean BG > 240 mg/dL, switched to BBI | The BBI group had better glycemic control compared to SSI. The BBI group had lower mean fasting BG (147 ± 36 vs. 165 ± 41 mg/dL, $P < 0.01^{***}$), lower overall mean BG (166 ± 32 vs. 193 ± 54 mg/dL, $P < 0.001^{***}$) The authors conclude that BBI is superior to SSI in non-critically ill patients with T2DM |
| Umpierrez (RABBIT 2 Surgery) (2011) [24] | RCT | $N = 211$ Patients with T2DM undergoing general surgery Included patients on low-dose insulin treatment at home (TDD ≤ 0.4 units/kg) | To compare glycemic control between BBI and SSI in surgical patients with T2DM | <i>BBI</i> : insulins glargin and glulisine using TDD 0.3–0.5 units/kg <i>SSI</i> : regular insulin four times daily for BG > 140 mg/dL. If mean BG > 240 mg/dL, switched to BBI BG target for both groups was 100–140 mg/dL | The BBI group had better glycemic control compared to SSI. The BBI group had lower mean fasting BG (155 ± 37 vs. 165 ± 40 mg/dL; $P = 0.037^{***}$), lower daily mean BG (157 ± 32 vs. 176 ± 44 mg/dL; $P < 0.001^{***}$), and more BG in target range (53 ± 30 vs. $31 \pm 28\%$; $P < 0.001^{***}$) Use of BBI reduced postoperative complications The authors conclude that BBI is preferred over SSI in surgical patients with T2DM |

Table 1.2 (continued)

| First author (year) | Study design | Study population | Primary objective | Intervention | Key findings |
|------------------------------------|----------------------------|---|---|---|--|
| Umpierrez (Basal Plus) (2013) [25] | RCT | <i>N</i> = 375 General medical and surgical patients with T2DM Included patients on low-dose insulin treatment at home (TDD ≤0.4 units/kg) | To compare glycemic control between BBI, basal plus SSI, and SSI in general medical and surgical T2DM patients | <i>BBI</i> : insulin glargine + pre-meal glulisine + glulisine SSI for BG >140 mg/dL; TDD 0.3–0.5 units/kg <i>Basal-plus</i> : insulin glargine (0.15–0.25 units/kg) + pre-meal glulisine SSI if BG >140 mg/dL <i>SSI</i> : glulisine SSI for BG >140 mg/dL BG target for all groups was 100–140 mg/dL | The percentage of BG in target range was higher in basal-plus (42%) and BBI (37%) compared to SSI alone (32%; <i>P</i> = 0.04***) SSI led to more treatment failures (>2 consecutive BG >240 mg/dL or a mean daily BG >240 mg/dL) compared to BBI or basal-plus There was no difference in hypoglycemia between BBI and basal-plus regimens |
| Midgal (2021) [26] | Retrospective cohort study | <i>N</i> = 25,813 31.4% treated with SSI alone. 15% of the SSI patients were transitioned to basal insulin Patients with T2DM under non-ICU care | To determine which patients with T2DM can be managed with SSI in non-ICU settings. The primary outcome was the percentage of patients achieving BG target | Patients were stratified according to continuous SSI use vs. transitioned to basal. Continuous SSI patients were further stratified according to admission BG and HbA1c BG target 70–180 mg/dL | For continuous SSI patients: 96% of patients with admission BG <140 mg/dL had a mean BG <180 mg/dL and 86% achieved BG target; 83% of patients with admission BG 140–180 mg/dL achieved BG target Only 18% achieved BG target in patients with admission BG ≥250 mg/dL (<i>P</i> < 0.001***) SSI may be adequate in patients with euglycemia upon admission |

RCT randomized controlled trial, *T2DM* type 2 diabetes mellitus, *BBI* basal-bolus insulin, *SSI* sliding-scale regular insulin, *TDD* total daily dose, *BG* blood glucose, *ICU* intensive care unit, *HbA1c* hemoglobin A1c

***Results were statistically significant

Landmark Inpatient Diabetes Studies

ICU Studies (See Table 1.1)

After the discovery of insulin, nonrandomized studies initially led to the use of remarkably high doses of insulin in DKA treatment [27, 28]. In 1935, a sliding scale of 20–100 units of subcutaneous (SC) insulin was typically given every half hour based on glucosuria. In 1949, an initial intravenous (IV) bolus of 200–400 units according to mental status changes was recommended, followed by IV boluses of 50 units every half hour until ketosis resolved [27, 29]. In the 1950s, there was a shift in management after a randomized study of 43 consecutive cases of DKA demonstrated that low-dose insulin was just as effective as a high-dose insulin approach in DKA resolution. The initiating doses of IV insulin were drastically higher than those of modern-day treatment where the low-dose protocol consisted of an IV bolus (80 units) followed by 0–80 units every 2 h, whereas the high-dose protocol consisted of a higher dose IV bolus (160 or 240 units) followed by 10–240 units every 2 h based on glycosuria and change in blood glucose. Glucose-containing fluids were only added when the blood sugar dropped to less than 300 mg/dL [30]. In 1973, Alberti et al. published the first successful management of DKA and HHS using low-dose intramuscular (IM) regular insulin where the cumulative insulin dose was less than 100 units at 24 h [16, 29].

In 1976, Kitabchi et al. published a prospective randomized clinical trial (RCT) in DKA treatment, which compared a low-dose intramuscular (IM) insulin protocol to a high-dose IV and SC insulin protocol in 48 patients with DKA [17]. The authors found that low-dose IM insulin at 0.1 unit/lb body weight sufficiently reduced plasma glucose <250 mg/dL using significantly less insulin (46 ± 5 vs. 263 ± 45 units). The rates of glucose reduction as well as DKA resolution were similar between the low- and high-dose groups. There were less hypoglycemia events and hypokalemia in the low-dose group compared to the high-dose group, where 25% of patients developed hypoglycemia [17, 28]. In 2004, Umpierrez et al. assessed the use of hourly SC insulin lispro compared to IV regular insulin infusion in DKA treatment. The treatment duration to achieve DKA resolution was similar between the groups [20, 28]. A meta-analysis of seven RCTs in 2016 showed no difference between SC and IV DKA treatment [31]. Further SC DKA treatment protocols using basal insulin and SC insulin every 2–4 h were developed during the COVID-19 pandemic in 2020 [32].

In ICU populations, the DIGAMI study, an RCT in 19 Swedish coronary care units (CCU) in 1995, evaluated 1-year mortality in DM patients with myocardial infarctions. Hyperglycemic patients, with and without DM, were randomized to either an insulin-glucose infusion protocol using a target glucose of 126–196 mg/dL, followed by multidose SC insulin for at least 3 months, or a conventional therapy, where patients did not receive insulin unless clinically indicated. At 3-month follow-up, the insulin-glucose infusion group had better overall glycemic control, and at 1 year, overall mortality was lower in the insulin-glucose infusion group

compared to the control group with a relative reduction in mortality nearing 30% [18].

The early 2000s led to several landmark inpatient diabetes trials in the ICU setting. The first important RCT by Van den Berghe et al. was in 2001, which evaluated the mortality of mechanically ventilated surgical ICU (SICU) patients receiving either intensive insulin therapy (target 80–110 mg/dL) or conventional therapy (target 180–200 mg/dL). The study reported a 42% ICU mortality risk reduction in the intensively treated group and significantly less in-hospital deaths compared to the higher glucose target group [19]. The Leuven Medical Trial in 2006 was an RCT in the medical ICU also conducted by Van den Berghe et al. which did not demonstrate the same results as the original SICU study. Using the same strict versus conservative glucose targets as the former trial, patients were randomized to either intensive insulin treatment or conventional therapy where an insulin infusion was only initiated once glucose exceeded 215 mg/dL. The Leuven Medical Trial found that intensive insulin treatment did not significantly reduce ICU or in-hospital mortality at day 3. Intensive insulin therapy did however reduce in-hospital mortality from 52.5 to 43% in patients who were in the ICU for more than 3 days ($P = 0.009$) and significantly reduced morbidity by preventing new acute kidney injuries and prolonged ventilation weaning [22].

In 2004, Furnary et al. described the findings of their prospective, nonrandomized study of patients with diabetes undergoing cardiac surgery known as the “Portland Diabetic Project.” The SC injection group received injections every 4 h to target glucoses less than 200 mg/dL using a sliding scale. The insulin infusion group used an initial glucose target of 100–150 mg/dL, which was adjusted over the study duration. Between 1987 and 1994, hyperglycemia ≥ 200 mg/dL within 48 h of cardiac surgery increased the risk of deep sternal wound infections by more than two-fold. The continuous infusion protocol reduced postoperative absolute mortality by an impressive 57%. While this was not a randomized trial, the findings are important: hyperglycemia ≥ 200 mg/dL and use of SC insulin regimens were associated with higher mortality after cardiac surgery, while postoperative insulin infusion protocols with tighter glucose targets led to lower rates of infection and cardiac-related death [21].

A shift in ICU glycemic management occurred in 2009 after the publication of the large-scale international Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation (NICE-SUGAR) randomized trial. Participants received insulin infusions and were assigned to intensive glucose control (target 81–108 mg/dL) or moderate glucose control (target 144–180 mg/dL). The number of deaths at 90 days was significantly higher in the intensive glucose control group compared to the conventional glucose control group (27.5% vs. 24.9%; $P = 0.02$). Severe hypoglycemia (≤ 40 mg/dL) also occurred more frequently in the intensive control group (6.8% vs. 0.5%, odds ratio 14.7; $P < 0.001$) [14]. The mortality outcomes contrasted with those previously published by Van den Berghe et al. [19]. The NICE-SUGAR trial was a much larger study across 42 hospitals, whereas the 2001 Van den Berghe et al. study was conducted at a single site. Additionally, the

Table 1.2 (continued)

NICE-SUGAR trial aimed to achieve lower glucoses in their higher glucose target group, which may have contributed to the overall difference in outcomes [14, 19]. The GLUCO-CABG trial by Umpierrez et al. (2015) randomized hyperglycemic patients receiving continuous insulin infusion to intensive (target 100–140 mg/dL) or conservative control (target 141–180 mg/dL) after coronary artery bypass surgery. The intensively treated group had significantly lower mean glucoses, but there was no difference in postoperative complications for DM patients. However, patients without DM did experience significantly fewer complications in the intensive group [23]. These studies ultimately led to a suggested glucose target for most critically ill DM patients to be 140–180 mg/dL, where 110–140 mg/dL may be considered in select patients such as after cardiothoracic surgery and in hyperglycemic patients without a prior history of DM [33, 34].

Non-ICU Studies (See Table 1.2)

The multicenter RABBIT 2 randomized trial sought to identify the best glycemic management in non-ICU patients with type 2 DM in 2007 [15]. Patients were randomized to sliding-scale regular insulin (SSI) four times daily or basal-bolus insulin (BBI). The BBI group had significantly better glycemic control compared to SSI at days 4–6 of treatment, lower mean fasting glucose, and lower overall mean glucose, and more patients achieved the glucose target (66% vs. 38%) without causing hypoglycemia. This study ultimately identified BBI as the preferred treatment approach and current standard of care for inpatient hyperglycemia in non-critically ill patients [15]. The RABBIT 2 Surgery multicenter trial in 2011 assessed glycemic management in general surgery patients with type 2 DM. Participants were randomized to BBI or to SSI four times daily using a glucose target of 100–140 mg/dL for both groups. The BBI group had better glycemic control with lower mean fasting glucose, lower daily mean glucose, and greater glucose in target range compared to SSI patients (Table 1.2). Composite postoperative complications, such as wound infection, pneumonia, bacteremia, and acute respiratory and renal failure, were much lower in the BBI group (8.6% vs. 24.3%, $P = 0.003$). Hypoglycemia (<70 mg/dL) was more frequent in the BBI group (23.1 vs. 4.7%; $P < 0.001$), but there was no difference in severe hypoglycemia (<40 mg/dL) (3.8% vs. 0; $P = 0.057$) [24]. The RABBIT 2 and RABBIT 2 Surgery trials clearly demonstrated that BBI is superior to SSI in non-critically ill medical and surgical patients with type 2 DM.

In 2013, the multicenter non-inferiority Basal Plus trial identified an alternative more personalized approach to glycemic control in non-critically ill patients with type 2 DM. Patients were randomized to BBI (insulin glargine, pre-meal glulisine,

and glulisine SSI), basal-plus (insulin glargine + glulisine SSI), or SSI for glucose >140 mg/dL using a target of 100–140 mg/dL (Table 1.2). Glycemic control and hypoglycemia rates were similar with BBI and basal-plus regimens, and both groups led to better glucose control compared to SSI [25]. A takeaway from this trial was that not all hospitalized patients need BBI. The best candidates for a basal plus correctional scale regimen include type 2 DM patients who are treated at home with only diet or oral medications, or who use <0.4 units/kg insulin daily, or if they have reduced oral intake [25].

There may be certain clinical situations that permit effective use of SSI. A large retrospective analysis of non-ICU patients with type 2 DM in 2021 evaluated SSI monotherapy [26]. Admission glucose <140 mg/dL was associated with 86% of patients reaching the target glucose range (70–180 mg/dL). Admission glucose of 140–180 mg/dL led to 83% achieving glycemic control, while admission hyperglycemia of 180–250 mg/dL and ≥ 250 mg/dL led to only 53% and 18% of patients reaching the glucose targets, respectively ($P < 0.001$). Thus, SSI may be effective for patients with mild hyperglycemia on admission but should not be used as monotherapy if there is hyperglycemia at hospitalization onset [26]. Additionally, SSI monotherapy should not be used for type 1 diabetes, severely uncontrolled diabetes (high hemoglobin A1c), or patients on insulin regimens at home.

Historical Overview of Key Inpatient Guideline Recommendations

Endocrine Society

The Endocrine Society was founded in 1916, initially dubbed “the Association for the Study of Internal Secretions,” later changing its name to what we call it today in 1952. The first set of clinical practice guidelines focusing on non-ICU inpatient hyperglycemia management was published in 2012, which were last updated in 2022. The 2012 guidelines focused on glucose goals, point-of-care (POC) glucose testing, and use of basal-bolus SC insulin regimens among other non-ICU topics [35]. The latest guidelines highlight recommendations involving the inpatient use of diabetes technology, such as continuous glucose monitoring (CGM) and hybrid closed-loop insulin pump therapy [36]. A summary of the current guidelines will be described further in Chap. 2.

American Diabetes Association

The American Diabetes Association (ADA) was founded in 1940 by a group of 12 physicians representing five local diabetes associations throughout the United States. The initial annual meeting occurred on June 1, 1941, in Cleveland, Ohio,

where more than 300 physicians from throughout the country attended leading to the development of different committees that founded what the ADA has become today [37].

The first set of ADA guidelines entitled “Standards of Care for Patients with Diabetes Mellitus” was published in May 1989. The position statement was brief, highlighting outpatient diagnosis and chronic management. Inpatient diabetes management was only reviewed while recommending involvement of a diabetes expert in hospitalized diabetes patients or during hyperglycemic emergencies [38]. The 2022 guidelines similarly emphasize the use of a glucose management team and provide recommendations on glycemic targets, CGM use, BBI or basal plus correction insulin regimens in non-critically ill patients, IV insulin use in the ICU, non-insulin treatment, glucocorticoid therapy, hypoglycemia, and discharge planning. A summary of the current guidelines will be described in more detail in Chap. 2.

American Association of Clinical Endocrinology

The American Association of Clinical Endocrinology (AACE) was founded in 1991 by 26 endocrinologists throughout the United States. The first meeting took place in April 1992 [39]. The first guidelines were published in 2006 and focused on outpatient diabetes management only [40]. In 2022, the updated guidelines included recommendations regarding inpatient management including CGM use, hypoglycemia, specialized diabetes teams, non-insulin agent use, ICU treatment and insulin infusion use, non-ICU care with a focus on a personalized approach, and discharge planning [34]. A summary of the current guidelines will be described in more detail in Chap. 2.

Historical Overview of Inpatient Diabetes Teams

Primary service teams have been traditionally responsible for inpatient diabetes management. Consultant diabetes teams are a newer concept. Since the 1990s, interdisciplinary diabetes teams have been studied as a beneficial tool for comprehensive glucose management to improve clinical outcomes [41, 42]. Specialized teams may involve endocrinologists, diabetes nurse and nurse practitioners, physician assistants, diabetes educators, pharmacists, and dieticians [43].

The use of inpatient diabetes teams leads to improved glycemic control [42]. In a randomized controlled study of 179 hospitalized patients with diabetes, 75% of patients who received input from a specialized diabetes team achieved goal glucose control (80–180 mg/dL), compared with only 46% in the control group [42]. More recently, a retrospective study of 1618 hyperglycemic patients on general medical wards demonstrated that active management by the specialized glucose management team consisting of endocrinologists and diabetes nurses led to significantly

lower overall mean glucoses and lower rates of hyperglycemia compared to the routine consultation approach where specialist input was only given if the primary team requested it [44].

In addition to improved glycemic control, specialized diabetes teams have been shown to have a financial benefit. A retrospective study of 756 patients with diabetes published in 2018 demonstrated a lower 30-day readmission rate in patients managed by a diabetes team compared to primary service team patients (22.5 vs. 32.4%, $P < 0.05$). Consulting the diabetes team within the initial 24 h of admission was associated with shorter hospitalizations, shorter lengths of stay, lower readmission rates, and reduced healthcare costs, which has also been demonstrated in other studies [45–48]. Further prospective studies are needed to assess the clinical and financial impact of specialized diabetes management teams.

Diabetes Technology

Diabetes technology in the inpatient setting represents an increasing area of innovation and research. For the first 50 years of insulin therapy, clinicians relied on indirect estimates of glycemia by measuring urinary glucose with Fehling's solution, a copper sulfate-based reagent [49]. The first blood glucose test strip was developed in 1965 and the first glucometer was introduced in the 1970s [50]. Advancements in diabetes technology including insulin pumps or continuous subcutaneous insulin infusion (CSII), CGM, and automated insulin delivery (AID) systems have occurred in the last two decades [51]. Inpatient technology use is still being studied.

The first prototype of an insulin pump was developed in 1963 by Dr. Arnold Kadish, with the initial patient studies occurring in the late 1970s [51–54]. Subsequent decades of technology advancements have led to modernization and increased use of the insulin pump. Advantages to ambulatory CSII are well documented and include improved glycemic control and lower rates of hypoglycemia in type 1 DM [55, 56]. Data involving inpatient use of CSII is limited, but major guidelines support the use of insulin pumps in the hospital for appropriate patients with the assistance of specialized diabetes teams [57, 58]. Continuing CSII use in the hospital has been associated with less severe hyperglycemia and less hypoglycemia [59].

The first CGM was approved by the Food and Drug Administration (FDA) in 1999 [50]. Since the early 2000s, there have been several CGM studies in general wards and ICU patients suggesting possible glycemic benefit, but the sample sizes are small and some findings have been inconsistent across studies [51]. The COVID-19 pandemic represented a unique time of innovation in inpatient diabetes history where CGM was used to assist with glycemic control while minimizing unnecessary direct patient contact. In April 2020, the FDA permitted inpatient CGM use during the pandemic [60]. Dexcom G6 CGM is feasible and accurate in COVID-19 patients, as well as in non-critically ill patients with DM, and can reduce recurrent inpatient hypoglycemia [61–63]. In 2020, Galindo et al. found that using

FreeStyle Libre Pro CGM in hospitalized type 2 DM patients receiving BBI was accurate, led to lower mean daily glucose, and improved hypoglycemia detection compared to point-of-care (POC) testing [64].

Artificial pancreas or AID systems are the latest innovations in diabetes technology. These automated systems involve algorithms which modulate insulin delivery according to sensor glucose data [57]. Closed-loop systems have been evaluated in hospitalized patients for the last two decades with promising results. Earlier studies assessed closed-loop systems in ICU patients and demonstrated that not only the use of AID systems was feasible in critically ill patients, but also controller algorithms could improve glycemic control without increasing hypoglycemia compared to standard SC insulin treatment [65–67]. More recent RCTs have evaluated AID systems in non-critically ill patients and have yielded similar results [68, 69]. Further details involving diabetes technology in the inpatient setting can be found in Chaps. 7 and 8.

Conclusion

As the prevalence of DM rises globally, clinicians must recognize the importance of hyperglycemia management in the hospital setting. Landmark trials have revolutionized inpatient diabetes care by providing data to optimize insulin regimens. Professional societies, specialized diabetes teams, and technology advancements allow for continued improved patient care. It is essential to appreciate the history of inpatient diabetes to recognize the challenges and successes of the past in order to improve patient outcomes in the future.

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Chapter 2

Current Standards of Care for Inpatient Type 2 Diabetes Mellitus



Naomi Friedman and Hanna J. Lee

Introduction

Diabetes mellitus is one of the most prevalent chronic diseases worldwide and is a growing global epidemic. In 2021, there were 537 million adults living with diabetes, and by 2045, this number is projected to reach 783 million adults [1]. There were an alarming 6.7 million deaths across the world due to diabetes in 2021 alone. According to the CDC's National Diabetes Statistics Report, 11.3% of the US population (37.3 million) have diabetes, among whom 23% are undiagnosed. Individuals with diabetes are more likely to be hospitalized and, in the USA, up to 25% of hospital inpatient days have been incurred by patients with a diagnosis of diabetes [2]. Reasons for admission range across various infections, including of the bone and soft tissues, vascular complications, and electrolyte disturbances, among many others [3]. In 2018 in the USA, 17 million emergency department (ED) visits among adults reported diabetes as a listed diagnosis. Among adults with diabetes, there were 248,000 ED visits for hyperglycemic crises (9.9 per 1000) and 242,000 for hypoglycemia (9.6 per 1000). Furthermore, in the USA, diabetes was the seventh leading cause of death in 2019 [4].

Inpatient hyperglycemia, independent of a prior diagnosis of diabetes mellitus, is associated with increased morbidity and mortality. A retrospective analysis of 2,030

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inpatients at a community hospital demonstrated that patients presenting with acute hyperglycemia experienced a higher in-hospital mortality rate of 16%, compared to 3% among hyperglycemic patients with a prior history of diabetes and 1.7% among normoglycemic inpatients without a prior history of diabetes [5]. Another study similarly showed increased rates of inpatient mortality among those admitted for a myocardial infarction who experienced stress hyperglycemia, with or without diabetes [6]. Furthermore, acute hyperglycemia itself has been independently associated with longer hospital stays, higher admissions to the ICU, and higher rates of sepsis, organ failure, and prolonged disability [5, 7]. Hyperglycemia at the time of admission has also been shown to be an independent predictor of mortality [8].

Likewise, hypoglycemia, defined as less than 70 mg/dL, has been a predictor of poorer outcomes [9–11]. Hypoglycemia can lead to acute cardiac and neurological complications and is associated with increased mortality [12]. A retrospective study showed that patients with diabetes presenting with hypoglycemia (defined by blood glucoses less than 55 mg/dL) and an acute coronary syndrome had at least a twofold increase in mortality at 2 years [12]. High-risk cardiac patients presenting with an ST-segment elevation myocardial infarction (STEMI) and with hypoglycemia (glucose <81 mg/dL) were similarly shown to have at least a threefold increased risk of death at 30 days [13]. Among critically ill ICU patients, intensive insulin therapy targeting glucose of 81–108 mg/dL led to significantly more hypoglycemic events (glucose <40 mg/dL) with an odds ratio of 14.7 and was associated with increased mortality (odds ratio of 1.14) compared to the standard-therapy group [14]. Observational studies have also demonstrated that the relationship between blood glucose levels and mortality is J-shaped in which glucoses of 100–156 mg/dL confer the lowest mortality risk [15, 16].

This chapter reviews key elements of the current society guidelines in the management of inpatient diabetes. The reviewed guidelines are primarily from the American Diabetes Association (ADA), the Endocrine Society, and the American Association of Clinical Endocrinology (AACE) [9–11]. We will highlight the diagnosis of hyperglycemia, treatment of hyperglycemia in the inpatient setting, and hospital discharge recommendations.

Diagnosis of Diabetes Mellitus and Hyperglycemia

For the aforementioned reasons, inpatient glucose control and appropriate management of diabetes and hyperglycemia are essential to reduce short- and long-term morbidity and mortality. In the USA, approximately 12–25% of noncritically ill hospitalized patients demonstrate hyperglycemia defined as a blood glucose >140 mg/dL [9]. The ADA and AACE guidelines recommend performing a hemoglobin A1c (HbA1c) on all admitted patients with hyperglycemia or a known history of diabetes, if not done within the past 3 months [10, 11]. An HbA1c value can help guide glycemic management decisions during a patient's hospital course. One group looked at the combined data from four randomized controlled trials (RCTs) of hospitalized patients with type 2 diabetes (T2DM) and discovered that higher HbA1c

values correlated with the need for higher doses of insulin and predicted overall worse hyperglycemia, despite gradual adjustments in inpatient insulin therapy [17]. The HbA1c additionally can guide how to optimize outpatient diabetes regimens at the time of hospital discharge and even provide insight into a patient's pre-admission glycemic status. For instance, the HbA1c can help differentiate inpatient stress hyperglycemia from undiagnosed diabetes [10, 11, 17, 18]. Although an HbA1c of 6.5% and above is a standard diagnostic criteria for diabetes, this threshold may be less sensitive among hospitalized populations with acute illnesses. One study reported that an HbA1c less than 5.2% reliably excluded a diagnosis of diabetes while an HbA1c above 6.0% had 100% specificity with an improved sensitivity of 57% for the inpatient diagnosis of diabetes [19]. Variations in erythrocyte survival due to anemia, hemoglobin variants, and chronic kidney disease (CKD), among other medical conditions, may limit the accuracy of the HbA1c, especially in the interpretation of glycemic variations shorter than 90–120 days [20, 21]. Alternative glycemic markers that complement the HbA1c and reflect glucose control during the preceding 2 weeks include serum fructosamine and glycated albumin; glycated albumin has been shown to be more concordant with changes in mean blood glucose than HbA1c or fructosamine [20].

Methods of Glucose Monitoring

Once patients with diabetes or hyperglycemia are identified, point-of-care glucose (POCG) monitoring is recommended to guide inpatient glucose management. The frequency of POCG checks should reflect the type and frequency of the individual patient's nutritional intake. POCG checks are typically recommended before each meal and at bedtime. If the patient is nil per os (NPO), monitoring is advised to be increased to every 4–6 hours [7, 10, 11, 22].

On April 1, 2020, the Federal Drug Administration (FDA) allowed for emergency use of continuous glucose monitoring (CGM) in the hospital setting [23]. Its utilization was prompted by the personal protective equipment (PPE) shortage during the COVID-19 pandemic in an effort to limit bedside POCG monitoring and to minimize the exposure risk to healthcare workers. CGM technology carries the additional advantage of showing projected glucose trends, allowing for the earlier detection of hypoglycemia and hyperglycemia than by POC monitoring [24]. Furthermore, the Dexcom G6 CGM system has been shown to have overall good accuracy with a mean absolute relative difference (MARD) of 12.8% among a heterogeneous population of noncritically ill inpatients [25]. With recent advancements in CGM technology and additional insights gained during its emergency allowance during the COVID-19 health crisis, the FDA granted the Dexcom G6 a Breakthrough Device Designation for inpatient use in March 2022. Although not an official approval, the designation is a significant step forward and will help facilitate the regulatory development, assessment, and review for CGM utilization in the hospital [26]. Currently, inpatient CGM utilization is investigational [9–11]. The Endocrine Society suggests that real-time CGM, if available, used in conjunction with

confirmatory POC glucoses can be considered in noncritically ill patients, treated with insulin, who have a particular risk for hypoglycemia. Glucose measurements and HbA1c are central to determining the initiation of hyperglycemic treatments, the incremental adjustments of inpatient diabetes therapy, and the tailoring of an individual patient's outpatient regimen at discharge.

Inpatient Glucose Targets

According to the ADA and AACE, it is generally recommended to maintain glucose for noncritically ill hospitalized patients in the range between 140 and 180 mg/dL, and the Endocrine Society advises a general target of 100–180 mg/dL [9–11]. It is, however, clearly essential to individualize the glycemic targets to a patient's comorbidities and risk for hypoglycemia including older age, low BMI, renal disease, liver failure, and tenuous nourishment status, among others. In these cases, it may be more prudent to liberalize the glycemic targets to avoid hypoglycemia. The glycemic targets are derived from RCTs that have shown, although with inconsistency, that tighter glycemic control reduced morbidity and mortality among ICU, surgical, and cardiac patients. A landmark study initially demonstrated benefits of intensive glycemic control (glucose targets of 80–110 mg/dL) with significant reduction in mortality among critically ill surgical patients [27]. However, a subsequent study in medical ICU patients did not mirror the reductions in mortality [28]. The pivotal NICE-SUGAR trial found no advantage to tighter glycemic control and instead highlighted a statistically significant association between severe hypoglycemia and mortality [14]. Further details regarding these studies can be found in Chap. 1. Overall, inpatient RCTs have shown conflicting results regarding mortality benefits with more aggressive glycemic targets and insulin therapy. Most studies nevertheless do demonstrate significant benefits in morbidity including reductions in septicemia, sepsis-related organ failure, earlier weaning from ventilatory support, and shorter hospitalization courses [29].

While these trials were done in critically ill patients in the ICU setting, this data has been applied to noncritically ill hospitalized patients. Although a universally shared inpatient target glucose range is not established, due to inconsistent conclusions from various studies, guidelines generally recommend a fasting, preprandial glucose target of 100–140 mg/dL with a postprandial glucose target of less than 180 mg/dL to avoid overt hypoglycemia and hyperglycemia [7, 10, 11, 22, 30].

Inpatient Pharmacotherapies for Hyperglycemia and T2DM

The standard therapy for hospitalized noncritically ill patients with diabetes and/or hyperglycemia is subcutaneous insulin therapy. After the publication of the Diabetes Control and Complication Trial and the United Kingdom Prospective Diabetes Study, two landmark trials that clearly highlighted the powerful microvascular

benefits of glycemic control, a renewed interest in insulin production led to the advent of insulin analogs [31–33]. The FDA approved, in 1996, the first rapid-acting insulin analog lispro, which has a fast onset of action of about 15 minutes and a duration of action of 4–5 hours. This was followed by the approval of the long-acting insulin glargine U-100 in 2000 which has a duration of action of approximately 24 hours. Additional subcutaneous rapid-acting, long-acting insulin, and even ultra-long-acting insulin analogs have since become available to target postprandial hyperglycemic spikes and basal insulin requirements, respectively [34]. These insulins have allowed for the more physiological basal-bolus dosing regimens and have predominantly replaced the short-acting regular and intermediate-acting NPH insulins for the standard, noncritically ill inpatient on a per os (PO) diet. Chapters 5, 27, and 28 will review the continued uses of regular and NPH (neutral protamine Hagedorn) insulins in special inpatient populations who are critically ill or receiving enteral or parenteral nutrition.

Non-insulin Pharmacotherapies

While insulin is considered the standard treatment for hospitalized patients with diabetes, there is emerging evidence for the use of non-insulin agents in hospitalized noncritically ill patients with T2DM. The Endocrine Society, ADA, and AACE recommend that oral agents such as dipeptidyl peptidase-4 (DPP4) inhibitors may be effectively used in select inpatients with T2DM [9–11]. A multicenter RCT demonstrated the noninferiority of the DPP4 inhibitor sitagliptin plus once-daily basal insulin to the basal-bolus insulin regimen among adult T2DM patients on the general medicine and surgical units [35]. Glycemic control, frequency of hypoglycemia, hospital length of stay, and in-hospital complications were comparable between the two treatment cohorts. Other studies with linagliptin and saxagliptin have likewise demonstrated the noninferiority and tolerability of DPP4 inhibitors among inpatients with mild hyperglycemia [36, 37]. Few studies have examined the efficacy and safety of glucagon-like peptide-1 (GLP-1) receptor agonists in the hospital setting. One RCT compared the glycemic effects of exenatide alone versus exenatide with basal insulin versus basal-bolus insulin among noncritically ill inpatients. The overall average daily glucose were higher in the exenatide-only group and were similar between the exenatide plus basal insulin and the basal-bolus insulin groups without differences in hospital length of stay [38]. Unsurprisingly, more nausea and vomiting were reported among patients treated with exenatide.

Other non-insulin therapies are generally not advised due to inadequate safety and efficacy data in the hospital setting [9]. Consensus guidelines caution the use of metformin in patients at risk for lactic acidosis, sulfonylureas due to its potential for prolonged hypoglycemia, and thiazolidinediones due to the risk for heart failure and fluid retention in the acutely ill patient [9, 10]. Clinically stable patients, however, in whom non-insulin therapies are anticipated as part of their outpatient diabetes regimen, may be carefully introduced to non-insulin medications prior to hospital discharge. More research is clearly needed to better determine the glycemic effects

and safety of non-insulin therapies in the hospital setting. Chapter 6 will review the role of non-insulin agents in the hospital setting in more detail.

Insulin Initiation

Due to insulin's more immediate and predictable pharmacokinetics, insulin is the standard of care in the inpatient management of hyperglycemia and diabetes. For most noncritically ill patients, a scheduled subcutaneous insulin regimen, often administered as a basal-only or a basal-bolus regimen, is recommended [9–11]. Such regimens typically include a once-daily long-acting insulin or a twice-daily intermediate-acting insulin (NPH or neutral protamine Hagedorn) that provides the basal, fasting insulin requirements. Occasionally, long-acting insulin is administered twice daily in patients who require significantly high doses of insulin. Bolus insulins are usually rapid-acting insulins that are administered before/with meals to minimize the anticipated postprandial hyperglycemia. The coordinated timing of the bolus insulin to the meal is important to avoid postprandial hyperglycemia and iatrogenic hypoglycemia. Rapid-acting insulins are therefore ideally administered approximately 15 minutes before the meal is consumed, while short-acting regular insulin is ideally administered 30 minutes before the meal [7]. As such, the bolus insulin is preferably administered when the meal tray is at bedside. The bolus insulin dose is determined based on the sum of both the nutritional component of the meal and an additional correctional rapid-acting insulin dose to proactively treat for any concurrent hyperglycemia.

When initiating a basal-bolus insulin regimen, the patient's weight, especially if insulin-naïve, can guide the initial insulin dose (see Fig. 2.1). The total daily insulin required commonly ranges between 0.2–0.5 U/kg [7, 30]. The weight-based calculation, however, may vary according to the patient's degree of insulin resistance, baseline glycemic status reflected by the HbA1c, dietary intake, and whether there is concomitant use of glucocorticoids, among many other factors. For instance, a more cautious approach with a total daily dose (TDD) of insulin less than 0.2 U/kg may be indicated in a frail, elderly patient who is new to insulin and presenting with acute kidney injury. On the other hand, a patient with an HbA1c greater than 10% and on high-dose dexamethasone may require a more aggressive weight-based calculation. A safe initial weight-based dose for the average patient with hyperglycemia is generally 0.4 U/kg. Approximately half the TDD is classically administered as the basal insulin dose while the other half is divided proportionately across the three standard meals of the day, if eating a PO diet [39]. If the patient is not insulin-naïve, the outpatient insulin regimen may be resumed but typically with at least a 20% dose reduction to account for differences in the consumption and the nutritional composition of hospital versus home food [7, 30, 39]. Furthermore, acute clinical variables including renal or hepatic dysfunction and changes in insulin sensitivity may necessitate more conservative dosing [41]. For enteral nutrition, the total daily insulin can similarly be distributed evenly between the basal and the

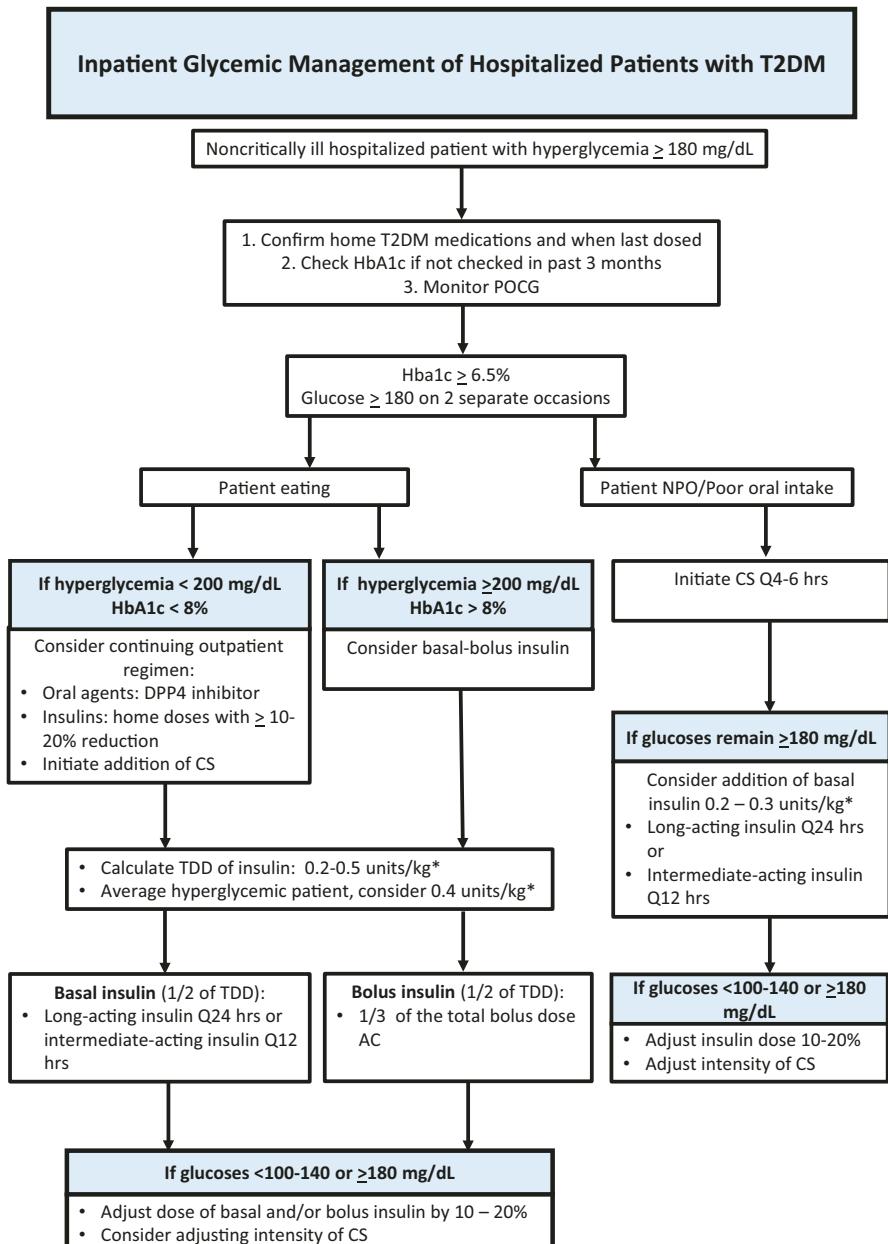


Fig. 2.1 Inpatient hyperglycemia treatment algorithm. *POCG* point of care glucose, *CS* correction scale, *CGM* continuous glucose monitor, *NPO* nil per os, *HbA1c* hemoglobin A1c, *TDD* total daily dose, *AC* ante cibum. *Adjust calculation based on insulin sensitivity and hypoglycemia risks (e.g., older age, renal or liver dysfunction, low body mass index, insulin naïve, etc.) [7, 9–11, 30, 39, 40]

bolus insulins. Depending on whether the enteral feeds are continuous or cyclical, the intermediate-acting NPH insulin, administered every 6–12 hours, or the short-acting regular insulin, administered every 6 hours, is commonly used to cover for the enteral nourishment [7, 30].

Insulin Titration

Inpatient subcutaneous insulin management is a dynamic process and requires continual reassessment and incremental dose adjustments to ensure that glycemic targets are safely achieved. If glucoses remain outside the target range, incremental adjustments by 10–20% of the insulin doses are recommended. Persistent fasting hyperglycemia, especially when characterized by an overnight glucose uptrend, suggests that an increase in the basal insulin is needed. Postprandial glycemic excursions, on the other hand, indicate that the bolus insulin dosing requires titration [7, 30] (Fig. 2.1). One common approach to address persistent hyperglycemia is to calculate the prior day's required total correctional doses and to accordingly up-titrate the standing insulin doses by distributing these additional units among the basal and bolus regimen. Alternatively, the total units of insulin, including basal, bolus, and correctional doses, administered in the prior 24 h can be tabulated and redistributed with approximately 50% as the new basal insulin dose and the other 50% as the bolus doses. Remember when calculating a 24-h total daily dose to only include 4 time points (e.g., breakfast, lunch, dinner, bedtime).

Hospitalized patients are frequently NPO for various studies and procedures. When nutrition is held, the basal insulin is continued but typically with a 20% dose reduction. In a patient who is overtly hyperglycemic, the dose reduction for NPO may be skipped. Holding basal insulin for NPO status is not recommended as the patient may develop severe hyperglycemia, potentially leading to cancellation of the planned procedure. The prandial, meal-based insulins are held for NPO, while the correctional insulin doses, administered at the timed POCG checks, are maintained to steer glucoses to target range. Consensus guidelines recommend close POCG monitoring while NPO, ranging every 4–6 h [9–11].

Correctional Dosing of Insulin

Additional correctional insulin doses of rapid-acting insulin are now standard components of inpatient diabetes management. These corrective doses provide an adjustable and an anticipatory strategy to correct for any pre-meal hyperglycemia. As such, the dosing is typically timed with each meal and at bedtime or, if NPO, every 4–6 h. The intensity of the “correction” scale is dictated by the degree of the individual patient’s insulin resistance. The original “1500 rule” calculation, based on regimens with regular insulin, estimated the correction dose by dividing 1500 by

the TDD of insulin [42, 43]. For instance, a TDD of 30 units would correlate with a correction factor of 50, signifying that 1 unit of bolus insulin would decrease the glucose by 50 mg/dL. Various iterations have since been developed, with distinct numerators often ranging from 1700 to 2000. Many institutions utilize pre-calculated sets of correction scales of varying intensity.

In contrast, “sliding”-scale insulins are reactive strategies in which a set of fixed doses of prandial insulin are administered often without consideration of the timing or the amount of nourishment intake or an individual’s insulin sensitivity. Historically, when capillary POCG testing became available in the 1970s, sliding-scale insulins were customary to inpatient care [44]. With several RCTs having since consistently demonstrated the superiority of basal-bolus insulin therapies, sliding scale-only regimens are discouraged [45]. Not only are sliding-scale insulins associated with up to a threefold increase in hyperglycemia, but they are also associated with increased rates of hospital complications such as pneumonia, bacteremia, wound infections, and acute renal and respiratory failure, compared to basal-bolus interventions [40, 46]. Furthermore, sliding scale-only regimens are reactionary, not meal dependent, and are nonphysiological. Currently, the Endocrine Society, ADA, and AACE recommend basal-bolus insulin therapy for the management of inpatient diabetes instead of sliding-scale regimens [9–11].

Discharge Planning

It is imperative to coordinate an appropriate transition of diabetes care from the inpatient to the outpatient setting. This requires that patients’ individualized preferences, abilities, and needs are addressed [9–11]. Specific needs to consider include whether a patient has the support necessary for continued diabetes management post-hospitalization and whether the plan is for discharge to home, assisted living residence, or other facility. Frequently, inpatient insulin regimens may need to be simplified to realistically meet the capacities of the patient. And in clinically stable patients, non-insulin treatments can be initiated for optimal transition to an outpatient regimen. Furthermore, insurance status and cost of medications should be assessed prior to discharge to ensure that the plan is feasible and sustainable for the patient.

A structured, comprehensive transition plan is recommended that includes diabetes self-management education. Patient knowledge of diabetes medication doses, medication administration techniques, glucose monitoring, hypoglycemia recognition and treatment, as well as healthy nutrition are paramount. There is evidence to suggest that, prior to discharge, education on diabetes “survival skills” improves glycemic control in the outpatient setting with a 1.25% HbA1c reduction at 3 months; this effect was even sustained at 12 months primarily in patients newly started on insulin [47]. One group proposed a discharge algorithm that is predicated on the admission HbA1c and effectively improved the HbA1c by ~1.5% at 4 months. Patients with an admission HbA1c less than 7.0% resumed their pre-hospitalization

diabetes medications at discharge. Other patients were discharged on their pre-admission oral diabetes medications plus a long-acting insulin dose at either a 50% reduction or a 20% reduction of the inpatient basal dose if the baseline HbA1c value was between 7.0 and 9.0% or above 9.0%, respectively [18]. More cautious intensification of discharge medications should be considered in elderly patients in order to avoid hypoglycemia [48]. Close coordination of care with a primary care physician, a diabetes education specialist, or an endocrinologist is especially advised for patients with hospital courses notable for hyperglycemia or hypoglycemia [9–11] (Fig. 2.2). For a detailed discussion of barriers faced during the transition from inpatient to outpatient care, please see Chap. 30.

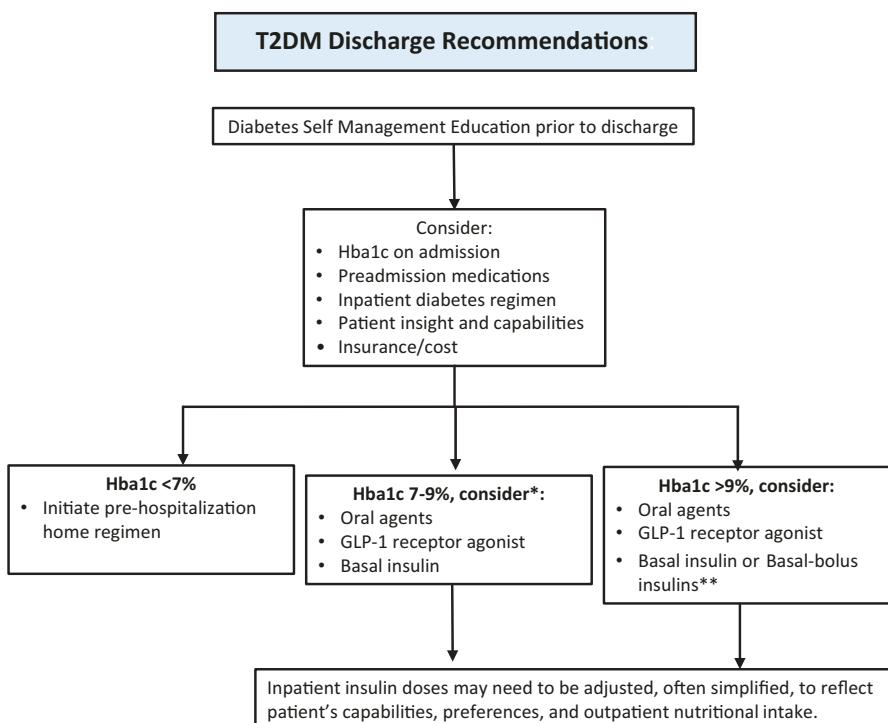


Fig. 2.2 Discharge recommendations for T2DM: *For less stringent HbA1c goals (i.e., elderly), consider resumption of home regimen [9–11, 18, 40]. **Insulin should be strongly considered in the discharge plan for patients with DKA, suspicion for possible type 1 DM, catabolic features (significant weight loss, cachexia, low body mass index)

Conclusion

T2DM is a major contributor to ED visits, hospitalizations, and increased morbidity and mortality. Hyperglycemia is commonly encountered in the acutely ill and is, even in the absence of a diagnosis of diabetes, associated with adverse events including cardiovascular complications, infections, organ failure, and prolonged disability. Although there is no universal consensus on specific inpatient glucose targets, avoiding hypoglycemia and glycemic excursions beyond 180 mg/dL improves clinical outcomes. Insulin is the mainstay of effective glycemic pharmacotherapy in the controlled hospital environment. For noncritically ill patients, subcutaneous insulin doses, which are typically weight based, are derived from multiple clinical factors including baseline HbA1c, nourishment status, presence of renal or liver dysfunction, concomitant medications, and inherent insulin resistance. Inpatient diabetes and hyperglycemia management is a dynamic process and requires proactive, incremental adjustments to scheduled basal plus correctional and basal-bolus plus correctional insulin regimens. Although more research is still needed to better define the role of non-insulin therapeutic agents in the hospital setting, select stable patients may benefit from the initiation of oral medications including DPP4 inhibitors. Despite these uncertainties, it is clear that inpatient hyperglycemia and diabetes cannot be ignored. A structured and comprehensive approach to inpatient diabetes management that begins with the prompt diagnosis of hyperglycemia at admission and ends with diabetes self-management education and appropriate outpatient diabetes planning is recommended.

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Chapter 3

Evaluation and Management of Inpatient Hypoglycemia



Paras B. Mehta, Esther Rov-Ikpah, and Robert J. Rushakoff

Introduction

Hypoglycemia in hospitalized patients has been associated with increased morbidity and mortality, early readmissions, increased length of stay, increased costs, and risk of discharge to a skilled nursing facility [1–4]. However, the cause and effect cannot definitively be established, and it is possible that hypoglycemia is a marker of illness severity rather than a cause of the negative sequelae. Indeed, multiple studies have noted that iatrogenic medication-induced hypoglycemia is not associated with increased mortality risk, and adjusting for comorbidities similarly suggests that hypoglycemia is an indicator of severe illness [5, 6]. Nevertheless, hypoglycemia will necessitate significant nursing interventions, and protocols to prevent and quickly treat hypoglycemia are required. Whether hypoglycemia is a cause or effect of severe illness, accurate identification and treatment are needed to prevent acute complications and end-organ damage that can result. This chapter describes the significance, risk factors, treatment protocols, and strategies for prevention of inpatient hypoglycemia.

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Current Definitions

Hypoglycemia is defined as a blood plasma glucose <70 mg/dL, which corresponds to the threshold for increases in counterregulatory hormones and the beginning of hypoglycemic symptoms [7]. “Severe” or “serious” hypoglycemia has been variably defined as glucose <54, <50, or <40 mg/dL based on studies that have shown worse outcomes and cognitive decline at these levels [8–10]. In 2017, the International Hypoglycemia Study Group recommended that all trials for glucose-lowering drugs report the incidence of glucose <54 mg/dL, as this was felt to be a reasonable threshold for clinically significant hypoglycemia [8]. More recently, in 2021, the Centers for Medicare & Medicaid Services initiated a new mandatory metric of severe hypoglycemia with harm, defined as a glucose <40 mg/dL within 12 h of administration of short-acting insulin or within 24 h of another antihyperglycemic agent, without a repeat glucose >80 mg/dL within 5 min of the hypoglycemic measurement [11].

Risk Factors

Beyond diagnosing and treating hypoglycemia in a timely fashion, in order to prevent hypoglycemia, it is important to identify patients who are at risk for developing hypoglycemia in the first place (Table 3.1). Overt risk factors include a history of hypoglycemia, tight or intensive glycemic control protocols, treatment with insulin or other glucose-lowering medications, or weaning/cessation of glucose-raising medications such as glucocorticoids or dextrose-containing fluids [7, 12–14]. Other commonly used medications that can lower glucose include beta blockers, fluoroquinolones, and angiotensin-converting enzyme inhibitors [15]. Disease-specific risk factors include those with type 1 diabetes (compared to type 2 diabetes), acute or chronic renal failure, liver disease, sepsis, or respiratory failure requiring mechanical ventilation [13, 14]. Nutritional risk factors include chronic malnutrition or low

Table 3.1 Hypoglycemia risk factors

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- History of hypoglycemia
 - Tight/intensive glycemic control protocols
 - Treatment with glucose-lowering medications (e.g., insulin, sulfonylureas)
 - Withdrawal of glucose-raising medications (e.g., glucocorticoids, dextrose)
 - Other medications (e.g., beta-blockers, fluoroquinolones)
 - Type 1 diabetes
 - Renal failure
 - Liver disease
 - Sepsis
 - Mechanical ventilation
 - Malnutrition
 - Low body mass
 - Advanced age
-

body mass index, abrupt or unexpected cessation of enteral feedings/caloric intake, or mismatch between insulin administration timing and caloric intake [7].

False Hypoglycemia: Importance of “Cleaning Data”

With the increased emphasis on reporting of inpatient hypoglycemia as a key metric, it is important to ensure true hypoglycemia when a low glucose result is seen on point-of-care glucose. The most accurate way would be to send a concurrent serum glucose laboratory check. However, practically speaking, this would take too much time to receive a result (and would unsafely delay hypoglycemia treatment). A potentially more pragmatic approach would be to repeat the point-of-care glucose within a few minutes to verify the prior result (if the patient is not experiencing hypoglycemic symptoms and has stable vital signs/mental status). If adapting this approach, data must be closely evaluated to ensure that hypoglycemia is not over-reported (e.g., multiple low glucose levels within a short time frame should be attributed to the same single hypoglycemic episode). When calculating hypoglycemia incidence, one proven approach is to eliminate any low glucose values for which another low value was reported 5 min earlier or 5–60 min later than the glucose value of interest [16]. In addition, if the immediate repeat glucose is not low, then the initial low glucose is considered a false low (for example, the first glucose is 35 mg/dL, but the repeat glucose in a patient who is awake and alert is 120 mg/dL). Finally, if the patient had not been on insulin or any other hypoglycemic medication in the 24 h prior to the event, then the low glucose should not be attributed to diabetes management and is more likely due to underlying medical issues (such as renal failure, liver failure, or sepsis). Hypoglycemia from causes other than diabetes is often seen and diagnosed by the presence of Whipple’s triad (low plasma glucose, symptoms of hypoglycemia, and relief of symptoms upon increase in plasma glucose). This subject is out of the scope of this chapter/textbook.

One must also be aware of pseudo-hypoglycemia, with a falsely low finger-stick glucose level due to decreased circulation [17, 18]. If such a phenomenon is suspected, the patient should be evaluated for etiologies such as peripheral vascular disease, vasospasm/Raynaud’s phenomenon, or cyanosis. A concurrent serum glucose should be checked to accurately evaluate blood glucose levels in such circumstances and determine if the glucose meter results are valid.

Hypoglycemia Treatment Protocols

With the implementation of electronic medical records, insulin order sets should be developed for the various anticipated patient populations, accounting for patient factors such as type of diabetes and presence/absence of caloric intake [19]. A hypoglycemia treatment protocol example in Table 3.2 should be embedded within every

Table 3.2 Examples of hypoglycemia treatment and prevention protocols

| Patient eating or NPO: treatment | | |
|--|--|---|
| Condition | Treatment | Glucose checks |
| Can take PO safely | <i>Glucose chewable tablet 20 g</i> 20 g, oral, every 15 min PRN, hypoglycemia For BG <70 mg/dL, administer to patient as first-line treatment for hypoglycemia if able to take PO safely | Repeat BG check and glucose tabs/juice every 15 min until BG ≥100 mg/dL |
| | <i>Juice (for hypoglycemia) 16 g</i> 16 g, oral, every 15 min PRN, low blood sugar, hypoglycemia **16 g = 4 oz. = 118 mL** | Repeat BG check and glucose tabs/juice every 15 min until BG ≥100 mg/dL |
| Not able to take PO safely | <i>Dextrose 50% injection syringe 12.5 g</i> 12.5 g, intravenous Every 15 min PRN, hypoglycemia For BG <70 mg/dL, only administer if the patient is strict NPO, or they cannot take PO safely | Repeat BG check and D50 every 15 min until BG ≥100 mg/dL |
| Patient on TPN or enteral feedings with interruption of feedings: prevention | | |
| Dextrose solution choice | Select “dextrose 10% water” or “dextrose 10% + 0.45% NS” as standard <i>Consider “dextrose 10% + 0.9% NS” for neurology/neurovascular/neurosurgery/sodium-wasting patients</i> | |
| If rapid- or short-acting insulin ordered (i.e., aspart, lispro, regular) | <i>IV fluid as per the above choice</i> For patients receiving aspart If TPN/TF are OFF, start IV D10 at the same rate of TF/TPN and discontinue D10 after 4 h | |
| If NPH ordered | <i>IV fluid as per the above choice</i> For patients receiving NPH Start IV D10 at the same rate of TF/TPN Stop D10 infusion 12 h from the last NPH dose or when TF/TPN is restarted | |

insulin order set, and the treatment protocol should include items such as frequency of repeated point-of-care glucose checks, intravenous dextrose administration (both boluses and maintenance fluids), and physician/provider notification parameters [20–22].

With the implementation of order sets, education for clinicians and nursing staff must also be provided to improve familiarity and comfort with placing and correctly executing the orders. Logistical and staffing limitations can make implementation of hypoglycemia treatment protocols difficult. Interventions to improve adherence have included the use of audible timers for repeat glucose measurements to decrease the memory burden on nursing staff [23]. Additionally, easily accessible inpatient diabetes training modules at our institution include content on hypoglycemia treatment protocols and general management strategies for hypoglycemia; hospitals and medical institutions should develop formal educational modules to ensure that all patient care providers are familiarized with hypoglycemia order sets and protocols.

Hypoglycemia Prediction Models

Hypoglycemia can often be predicted with the implementation of thoughtful algorithms. Several algorithms have been published with promising results. Inputs/predictors of hypoglycemia often include identification of high-risk patients based on demographics, anthropometrics, medications, inpatient diagnoses, and comorbidities, as well as those with decreasing glucose values [24–26]. Additionally, incorporating a hypoglycemia prediction tool at the time an insulin order is placed can help predict hypoglycemia over the subsequent 24-h period [27]. Consistent examples of patients at higher risk for hypoglycemia are those on insulin with previous hypoglycemia or glucose <90 mg/dL, on sulfonylurea agents, and with renal failure. With the growth of machine learning, it appears that algorithms based on machine learning may outperform those based on logistic regression models [28].

Continuous Glucose Monitoring in the Inpatient Setting

With the increased use of continuous glucose monitors (CGMs) in the outpatient setting, many hospitalized patients come into the hospital setting wearing their own CGM device. This can provide a unique opportunity to capture more data than is typically available with point-of-care glucose testing (which is the usual glucose monitoring modality done on hospitalized patients). While promising, data from CGM studies have offered mixed results with regard to accuracy in the inpatient setting [29, 30].

Earlier studies about CGM use in hospitalized patients found that some CGMs were only able to capture hypoglycemia in 50% of the documented episodes seen on point-of-care glucose testing [31]. Lee and colleagues found that while CGMs demonstrated good clinical accuracy and correlated with capillary glucose levels, real-time hypoglycemia detection ability in situations involving the management of critically ill patients in the emergency department was limited [32]. Another study showed that while CGMs were accurate and comparable in patients with normoglycemia and hyperglycemia, they were less accurate in the hypoglycemic range [33]. More recently, Davis and colleagues found that CGM accuracy could be lower when patients are hypoglycemic with glucose <70 mg/dL, as well as in other clinical scenarios such as severe anemia [34].

As described in Chap. 8 focused on CGM, as the infrastructure for inpatient use of CGM becomes available, CGM will be a useful tool for prevention of hypoglycemia.

Documentation

With hypoglycemia treatment, appropriate documentation is necessary to ensure that the treatment interventions are captured adequately and accurately to not only document a patient's response to the treatment given, but also ensure that this data is accessible to all members of the treatment team. Most, if not all, electronic health records (EHRs) have various places to document hypoglycemia treatment information, such as in a provider notification tab, in a flowsheet, and even on the electronic medication administration record (eMAR). However, wherever this information is documented, there must be an element of integration into the appropriate insulin/glucose management flowsheet in order for this data to be useful to the clinician in real time. Leveraging the EHR to allow a display of pertinent information relating to glycemic management may be helpful to identify trends and patterns.

Documentation for nursing should include a description of patient symptoms and the treatment modality chosen (e.g., juice, glucose tablets/gel, or intravenous dextrose) and the amount of carbohydrates used. For patients who cannot safely take oral glucose-containing tablets, gel, or liquids, and do not have intravenous access, glucagon nasal spray or subcutaneous or intramuscular glucagon can be used. Documentation should capture the elements of the hypoglycemia treatment protocol utilized and should capture the patient's symptomatic response to the treatment. Identifying the cause of hypoglycemia may help reduce the recurrence of hypoglycemia, and in one study, hypoglycemia rates decreased after an automated tool was implemented which elicited a response from the nurse about the cause of the hypoglycemia event [35].

Prevention

As previously mentioned, hypoglycemia in acutely ill hospitalized patients is associated with worse outcomes. One study found that over half of hypoglycemia cases in the hospital were potentially preventable, such as prescribing insulin regimens that do not conform to best practice standards, failure to appropriately identify and mitigate the source of the initial hypoglycemia event, and a failure to appropriately respond to unexpected interruptions of nutrition in a patient receiving nutritional insulin [36]. A summary of strategies that may be used for prevention of inpatient hypoglycemia is presented in Table 3.3.

Prevention of hypoglycemia not related to medication administration, but rather disease-specific factors, could be approached by instituting accurate monitoring and early identification of high-risk patients such as those with malnutrition and kidney or liver disease, with or without a diabetes diagnosis. For these patients, accurate monitoring with scheduled, frequent point-of-care glucose checks with standing hypoglycemia protocol treatment orders in place can be beneficial.

Table 3.3 Strategies for hypoglycemia prevention

-
- Identification of patients at high risk for hypoglycemia [renal failure, hepatic failure, poor nutrition, previous hypoglycemia, high-dose insulin (generally >0.5 units/kg)]
 - Institutional standardized monitoring protocols (e.g., electronic order sets) and hypoglycemia prediction models
 - Medication instructions (e.g., hold parameters)
 - Perioperative protocols for adjusting insulin doses
 - Avoidance of oral hypoglycemic agents in inpatient setting (e.g., sulfonylureas)
 - Standard protocols for initiating IV glucose infusion when TPN or enteral feedings are interrupted
 - Post- or mid-meal insulin dosing to adjust the meal insulin for actual consumption
 - For meals on demand (where patients can order food at will), limit the meals and insulin so a minimum time period between meals (and insulin) exists to decrease the risk of “stacking” of insulin (i.e., breakfast at 9 a.m., lunch at 11 a.m.—insulin at both times)
 - For type 2 diabetes patients on insulin as outpatients, decrease doses to 70–80% of outpatient dose on admission
 - For patients on longer acting basal insulin (i.e., degludec), consider decrease to <70% of home basal insulin (if using glargine, for example) as the longer acting insulin will still be on board
-

For medication-associated hypoglycemia such as insulin, prevention should take a multipronged approach. As above, one approach is using structured protocols in the form of order sets for inpatients receiving insulin for glycemic management [7, 35]. Patients on enteral nutrition or parenteral nutrition receiving insulin should have automatic dextrose infusion orders with parameters for infusing dextrose (such as if enteral/parenteral nutrition is unexpectedly interrupted and the patient has received a rapid-acting insulin that would still be within its duration of action). Having a standing dextrose infusion order will prevent any delays requiring ad hoc orders and facilitate starting dextrose infusion when deemed necessary.

Clear medication instructions that are not overly complicated may also be useful with regard to when a nutritional dose of rapid-acting insulin should be held (e.g., if there is a planned interruption of an enteral feeding at midnight in anticipation of an early-morning procedure). Also, instructions to only administer nutritional insulin when meals are present and a patient is ready to eat (if using rapid-acting insulin) may help prevent a mismatch in the timing of administration of nutritional dose and potential hypoglycemia event from receiving a nutritional dose of insulin before a meal is available [37]. In addition, the glucose check to determine the meal insulin dose should be done at the time the meal is present and insulin will be given. Having a glucose check at a different time can be problematic. The practice of defining hold parameters for hypoglycemia-causing medications under the defined conditions may help remove any barriers, or perceived barriers to nursing staff about when to hold medications. Oral agents that can provoke hypoglycemia (sulfonylureas and meglitinides) should generally be avoided in the inpatient setting though if using the short-acting meglitinides, the risk for hypoglycemia can be reduced if the medication is not given when the patient will not be eating. In addition, premixed insulins, such as 70/30 mixtures, have been associated with inpatient hypoglycemia [38].

Education

Education of providers and nursing staff may be another important tool to use in preventing inpatient hypoglycemia. Standardized education and competency should be assessed in providers who are involved with insulin ordering/prescribing, preparing, and administration such as nurses, pharmacists, and physicians [7, 37]. Education of patients about hypoglycemia signs and symptoms is also important. Educating nurses about when to notify a provider will help prevent repeated hypoglycemia related to medication administration. For example, if a mealtime or basal dose is too high and the nurse repeatedly administers such a dose without a modification, hypoglycemia can recur. Nurses should also be aware of when to notify a provider about a hypoglycemia event. These notification parameters can be attached to all insulin order sets and be automatically ordered along with the insulin. System-related factors such as understaffing should also be addressed to minimize delays in identification and management of hypoglycemia [7].

Glucometrics

System-wide monitoring of hypoglycemia trends across the hospital should be done, with special attention to insulin dose-related hypoglycemic events. If found, plans for addressing system-related barriers should be implemented with continual iterative re-evaluation based on hypoglycemia trends [7].

Future Considerations

Patients are now often on once-per-week GLP1 receptor agonists, and depending on the timing of the last dose, the effects could be gone or last for a week at the time of admission. The glucose-lowering effects of the SGLT2i may last for a week, and if discontinued on admission, the effects will wane over the next few days. In addition, as mentioned above, the glucose-lowering effects of longer acting basal insulin may still be active. As very-long-acting basal insulin becomes available (once-per-week basal, for example), the effects of that insulin will be present. Thus, at the time of admission and for several days after that, a patient may be at high risk for hypoglycemia depending on the doses of all these medications and the patient's nutritional state.

Conclusion

Given the association of inpatient hypoglycemia with increased morbidity and mortality, prevention, early identification, and timely treatment are paramount. Patients at high risk of hypoglycemia should always be identified and monitored closely. Advancements have been made in cleaning hypoglycemia data (to have accurate reports on institution rates of hypoglycemia), hypoglycemia prediction models, and treatment protocols, and further improvements in these facets should continue to be explored. Technological advances such as continuous glucose monitoring and system-wide glucose monitoring through electronic medical records also provide additional avenues for optimization to decrease the rates of inpatient hypoglycemia.

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Chapter 4

Inpatient Type 1 Diabetes



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Introduction: Global Incidence and Prevalence of Type 1 Diabetes

There is a scarcity of studies and conflicting data about the worldwide incidence and prevalence of type 1 diabetes mellitus (T1DM). The common denominator among studies is that the number of newly diagnosed cases (incidence) and the total number of existing cases of T1DM (prevalence) are on the rise [1–4]. The rise in the incidence and prevalence of T1DM is multifactorial and has been attributed to various factors such as geographic location (region, country, or continent), income level (low-, middle-, or high-income countries), ethno-racial origin, age, life and environmental factors (maternal diet, Cesarean versus vaginal delivery, breastfeeding versus bottle-feeding, childhood nutrition, microbial exposure, use of antibiotics, pollution) [1–4]. Due to the heterogeneity of study methodologies, further validation research studies are needed. It is beyond the scope of this book chapter to delve into the analysis and validation of these studies.

In 2017, according to the Global Burden of Disease Study, there were about 23 million individuals living with T1DM in the world [5], yet according to the World Health Organization (WHO), there were about 9 million individuals with T1DM [6]. The International Diabetes Federation (IDF) estimates the prevalence of T1DM

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to be about 10% of all diagnosed cases [7]. Due to increased life expectancy, more than 60% of all those living with T1DM in the world are above the age of 40 [2]. The prevalence of T1DM is tenfold higher in high-income countries (HICs) compared to lower income countries (LICs) [2]. However, those living in underdeveloped and developing countries are expected to be more negatively impacted by suboptimal diabetes care [1].

It is paramount to mention that social determinants of health (SDOH) inequities may increase the risk for acute diabetes emergencies (severe hypoglycemia, DKA, HHS) in vulnerable populations. Safety-net hospitals may encounter and treat a higher volume of patients from ethno-racial minorities with T1DM. In a 2-year T1DM observational retrospective longitudinal electronic health record (EHR) study, resource utilization for diabetes emergencies was more likely in African Americans with an HbA1c >7%, who were uninsured or underinsured, who were smokers, and who were with additional comorbidities (obesity, hypertension, and depression) [8].

Overall rising global trends in the incidence and prevalence of T1DM as well as the increased life span of those living with diabetes call for specialized inpatient glycemic management teams. This chapter focuses on the needs of the inpatient population with T1DM and how specialty care teams comprised of endocrinologists, hospitalists, certified diabetes care and education specialists (CDCESS), board-certified advanced diabetes managers (BC-ADMs), advanced practice providers (APP), endocrinology fellows, pharmacists, wound ostomy and continence nurses (WOCNs), financial counselors, case managers, and medical social workers (MSWs) collaborate for optimization of care and mitigation of disease burden.

T1DM, Differential Diagnosis, Caring for T1DM in the Hospital Setting

In 2021, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) jointly released a consensus report about T1DM management for those aged 18 years and above [9]. New-onset T1DM in adults may have either an acute or a slower onset, which can lead to a misdiagnosis of T2DM. Conversely, monogenic diabetes types can be mistakenly diagnosed as T1DM. Pancreatic/pancreatogenic diabetes (type 3c) and CIADM/ICI-DM are also differential diagnoses. CIADM/ICI-DM will be discussed ahead in this chapter. A mixed or atypical clinical picture may lead to erroneous diabetes type at the time of diagnosis with long-term implications related to education, diabetes regimen, access to wearable technologies, and psychosocial support. About 40% of those aged 30 and above are mistakenly diagnosed as having T2DM [9]. Latent autoimmune diabetes of the adult (LADA) may present with characteristics of either or both T1DM and T2DM and be mistaken for either type. LADA may also be known as type 1.5 diabetes with slow progression to total insulin replacement [10].

An algorithm for those suspected to have T1DM has been developed with available data from a white European population [9]. If T1DM is suspected, autoantibodies are to be measured starting with GAD65. For those who are GAD65 negative, islet tyrosine phosphatase 2 (IA2) and/or zinc transporter 8 (ZnT8) assessment should follow. The algorithm does not recommend the measurement of islet cell antibody (ICA). Worthy of mention is that about 5–10% individuals of white European descent who test negative for autoantibodies do have T1DM. In addition, antibodies also vanish over time, and in those who have been diagnosed over 3 years ago, measuring the C-peptide level is recommended. If T1DM is clinically suspected, an individual should be treated as having T1DM, or under supervised conditions, a period without insulin could be trialed. Monogenic diabetes should be ruled out in those <35 years [9]. Nonetheless, for those of non-white European descent, differential diagnosis may be challenging as this present algorithm cannot be extrapolated to the general population and all ethnicities. Moreover, it is important to mention that the risk for autoimmune thyroid disease, vitiligo, or celiac disease is increased in those with T1DM [11]. Table 4.1 provides an overview of the typical features and suggested testing for the various types of diabetes as per the classification and diagnosis of diabetes [12]. These guidelines are not a substitute for consulting with a diabetes specialist.

Hyperglycemic Crises and T1DM

The expedited diagnosis of DKA and/or HHS is fundamental for the soonest possible resolution as illness severity may lead to increased mortality risk. It is recommended that every patient with T1DM who experiences an acute illness be promptly assessed and treated following a standardized algorithm. DKA treatment calls for insulin, fluid, electrolyte replacement, and identification and treatment of the precipitating factor, yet divergent approaches among providers and organizations can lead to suboptimal management. It is paramount that standardized treatment guidelines, protocols, and insulin computerized provider order entry (CPOE) sets be available. DKA precipitating factors in T1DM include but are not limited to omission/missed basal insulin, infectious/disease process(es), insulin access issues (uninsurance, underinsurance, household income), substance abuse, and mental illness. Novel risk factors for DKA may also include COVID-19-positive patients, use of off-label SGLT-2 inhibitors in T1DM, and CIADM [13].

For insulin management, there are both homegrown glycemic management systems as well as commercially available ones such as the Glucommander™, EndoTool software, GlucoStabilizer™, and GlucoCare™ [14]. Algorithm-driven insulin infusion computer calculators (IICCs) present many advantages compared to paper protocols such as increased staff satisfaction, improved adherence, increased glucose time in range, and decreased glycemic variability [15].

Once the hyperglycemic emergency is resolved, transition from IV insulin infusion to a subcutaneous insulin regimen or to the patient's own insulin pump should

Table 4.1 Diabetes type features

| Parameter | T1DM | LADA/type 1.5 | T2DM | CIA DM/ ICL-DM | MODY | Pancreatic/ type 3c | CFRD | NODAT/ PTDM |
|--|--|--|---|-------------------------------|--------------------------------|-------------------------------|--------------|-------------------------------|
| Onset | Most <35 years | Adults; slower progression than T1DM | Mostly adults | Fulminant | <25 years | Mostly adults | Young adults | Adults |
| Prevalence | 5–10% of all cases | ~1/3 of cases of T1DM | 90–95% of all cases (higher prevalence in African Americans, native Americans, Hispanic/Latinos, Asian Americans) | Less common | 2–5% of cases | Less common | Less common | Less common |
| Family history/genetic predisposition | Less common | Less common | Common | NA | Yes (autosomal dominant) | NA | Less common | NA |
| β-Cell autoimmunity | Yes | Yes | No | Yes | No | No | No | No |
| Autoimmune disease history | More common (personal or family history) | More common (personal or family history) | Less common | NA | NA | NA | NA | NA |
| Autoimmune markers (ICA, IAA, GAD65, IA-2, IA2β, ZnT8) | Positive | Positive | Negative/low | Positive in <50% of cases | IAA negative; normal C-peptide | Negative | Negative | Negative |
| Plasma C-peptide | Low or absent | Low or absent | Variable (initially high, then normal/low with disease progression) | Low or absent | Normal | Low or absent | Variable | Variable |
| Ketosis prone | Common | Possible | Seldom | Possible | Unlikely | Possible | Possible | Varies |
| Overweight (BMI 25.0–29.9 kg/m ²) | Similar to general population | Similar to general population | Common (some Asians with T2DM do not meet overweight criteria) | Similar to general population | Similar to general population | Similar to general population | Less common | Similar to general population |
| Obesity (BMI ≥30 kg/m ²) | | | | | | | | |

CIA DM/ICL-DM checkpoint inhibitor-associated diabetes mellitus, *CFRD* cystic fibrosis-related diabetes, *GAD65* glutamic acid decarboxylase autoantibodies, *IAA* insulin autoantibodies, *IA-2 and IA2β* tyrosine phosphatases islet antigens, *NODAT* or *PTDM* new-onset diabetes after transplant/posttransplantation diabetes mellitus, *ZnT8* Zinc transporter 8 autoantibodies

take place. In patients with T1DM, the transition from IV to subcutaneous insulin can be particularly challenging as the timing and coordination of each step are critical for success. The basal insulin should overlap with the IV insulin for 1–2 h or alternatively an overlap bolus can be used. In addition, the insulin drip and dextrose-containing IV fluids should be discontinued at the same time to ensure that the dextrose-containing IVFs do not continue after cessation of insulin infusion and lead to severe hyperglycemia and potentially reopening of the anion gap. The timing of the first meal and mealtime insulin should also be coordinated as mismatches can be detrimental, especially in patients with T1DM. Please refer to Chaps. 5 and 11 Diabetes in the Critically Ill Patient: DKA, HHS, and Beyond and Diabetes Management in the Emergency Department.

Inpatient Glycemic Targets

The 2021 ADA and the EASD joint consensus recommends a glucose target range between 140 and 180 mg/dL (7.8–10 mmol/L) for most non-critically and critically ill adult hospitalized patients [9]. The recently released 2022 American Association of Clinical Endocrinology (AACE) practice guidelines also recommend an inpatient glycemic target between 140 and 180 mg/dL for the nonpregnant inpatient adult population [16].

By 2025, it is expected that CMS payments will be tied to electronic clinical quality measures (eCQMs) including hospital hypoglycemia and hyperglycemia rates. To help guide quality improvement efforts in improving inpatient glycemic control, the Society for Hospital Medicine (SHM) offers a no-cost Glycemic Control Implementation Guide [17]. In addition, the National Healthcare Safety Network (NHSN), which is the largest healthcare event tracking system in the USA, is creating a platform with metrics that align with the new Centers for Medicare and Medicaid Services (CMS) eCQM measures for hyper- and hypoglycemia that link inpatient blood glucose results with EHR medication data to help hospitals collect medication-related data, improve patient safety, and promote quality improvement efforts [18].

Wearable Technology: Continuous Subcutaneous Insulin Infusion (CSII) or Insulin Pump Therapy (IPT) and Continuous Glucose Monitoring (CGM)

As T1DM incidence and prevalence continue to rise, so will the number of patients who wear insulin pumps and continuous glucose monitoring (CGM) devices. It is expected that the use of insulin pumps and CGMs in the hospital setting will also increase. Therefore, guidelines need to be in place for the safe use of these devices

in the hospital setting. Institutional guidelines and/or policies and procedures that delineate step-by-step workflows ensure that healthcare provider, hospital staff, and patients' responsibilities are followed [19].

The 2021 ADA and EASD joint consensus advocates for the safe use of insulin pumps and CGM devices for patients with T1DM in the hospital setting [9]. It also recommends the oversight by a diabetes specialty team that provides ongoing glycemic management as well as diabetes self-monitoring, education, and support (DSME-S) to patients and family/caregivers, and transition planning for the outpatient setting. It underscores the importance of having guidelines in place for the selection of appropriate patients [9]. Patient selection criteria would include those who have no cognitive impairment and are able to demonstrate DSME competence [9, 20].

Available automated insulin delivery (AID) systems in the USA include the MiniMed 780G system (USA)/Guardian glucose sensor and transmitter via SmartGuard algorithm, Tandem Control-IQ system (USA)/Dexcom G6 glucose sensor and transmitter via Control-IQ algorithm, and the tubeless Omnipod 5/Dexcom G6 system. Worldwide AID systems also include the Dana insulin pump (Korea)/Dexcom G6 glucose sensor and transmitter via Android-enabled CamAPS FX application and the Kaleido insulin pump (France)/Dexcom G6 [21]. Most recently, "looping" or Do It Yourself (DIY) open-source closed-loop non-FDA-approved device activists and users of AID systems have emerged. The #WeAreNotWaiting is a global activist digital engagement of individuals living with T1DM [22]. It is essential for those directly involved in the management of T1DM patients to have a working knowledge of the predominantly used devices and/or have access to a diabetes team for the safe use of these devices in the inpatient setting.

CGM therapy benefits include but are not limited to providing glucose values with directional arrows indicating a rise or fall in glucose trend, glucose variability, and also prediction and detection of alerts/alarms for hyperglycemia and hypoglycemia. CGM therapy is an adjunct to diabetes management, and it is approved for outpatient use [19]. CGM reliability in the noncritical care units was found to be acceptable between point-of-care testing (POCT) blood glucose (BG) and CGM sensor glucose as well as serum glucose and CGM values [23]. CGM therapy got provisional approval for use in the critically ill during the COVID-19 pandemic [24]. Among some of the challenges to using CGM therapy in the critically ill are impaired tissue perfusion, tissue biofilm, sensor drift, and drug interference (acetaminophen, maltose, ascorbic acid, dopamine, mannitol, heparin, uric acid, salicylic acid) [24]. The scarcity of CGM studies in both non-ICU and ICU settings calls for further investigation. In the non-ICU setting, CGM has demonstrated superiority in detecting hypoglycemia, but non-blinded CGM studies are needed for T1DM in the ICU setting [25]. The increased use of inpatient CGM therapy during the COVID-19 pandemic has increased both the experience and available data, which will help pave the way for future inpatient use. In the 2020 global expert panel consensus by the Diabetes Technology Society, the value of CGM therapy is acknowledged and the need for further research is underscored [26]. The AACE clinical practice

guidelines recommend either real-time or intermittent CGM for all those living with T1DM. It also addresses the usefulness of CGM systems in the inpatient setting leveraged by protocols and procedures [16].

Given the rise in the prevalence and incidence of T1DM, the use of wearable diabetes technology is also expected to increase in the hospital setting. The German- and Austrian-based Diabetes Prospective Follow-up (DPV) observational study with 96,547 patients (53% males including children, adolescents, adults with median age of 17.9 years) demonstrated that the use of insulin pumps among T1DM has increased from 1% in 1995 to 53% in 2017 and the use of CGM has increased from 3% in 2006 to 38% in 2017 [27]. Study authors add that the increase in the use of wearable technology is corroborated by population-based studies in Nordic countries, Canada, and the USA [27].

The use of insulin pumps in the USA has exponentially increased from less than 7,000 in the 1990s to over 350,000 users [28]. The use of insulin pumps has increased among patients admitted to acute care settings [29]. On June 6 at the 2022 ADA 82nd Scientific Sessions, the T1D Exchange Team delivered an oral presentation regarding the online longitudinal US study registry (the T1D Exchange Registry including both adults and children with T1DM), in which the use of AID, insulin pump without AID, and multiple daily injections (MDIs) was 26.4%, 43.6%, and 30%, respectively [30].

It is recommended that protocols, guidelines, and providers' orders be available with established policies and procedures that include, but are not limited to, the frequency of BG POCT, nutrition plan and/or diet order, basal insulin rate(s), insulin-to-carbohydrate ratios (I:CHO), and insulin sensitivity/correction factor (ISF). It is essential to have a team of diabetes experts well versed in all the commercially marketed insulin pumps and CGM devices available to their patient population [9, 19, 31, 32].

Insulin pump setting adjustments are made necessary, but not limited to those with AKI, with prolonged NPO, or receiving corticosteroids. In addition, there are special considerations in which wearable technology should be discontinued, such as for patients with altered mental status or inability to manage the pump and those expected to undergo imaging studies (MRI, CT scan, and X-ray), diathermy, and hyperbaric chamber therapy. In the critically ill, transition to intravenous (IV) insulin drip is recommended [24].

When patients on wearable technology prior to admission are treated for DKA and HHS and are ready to transition off the insulin drip, they could either resume their insulin pump and/or CGM or receive subcutaneous insulin (basal, nutritional, correction). It is recommended that the first transitional long-acting insulin injection overlap with the IV insulin drip for 2 h (or overlap bolus administered) prior to discontinuing it to avoid ketonemia and reopening the anion gap (please refer to Chap. 5 for diabetes in the critically ill patient, DKA, and HHS). Alternatively, if patient readiness is verified and insulin pump supplies are available, transition to the insulin pump while in the hospital setting is recommended.

Patients who remain on subcutaneous insulin injections until discharge and do not have insulin pump supplies will need to be instructed on how to safely transition

back to their insulin pump the next day at home. The most common scenario is that these patients will receive an injection of basal insulin (glargine) on the day of discharge and are able to fully transition back to their pump on the same day by setting a temporary basal rate on their insulin pump for the next 24 h from the last dose of glargine received at the hospital. In this case, they will also need to bolus for meals (carbohydrates) via the insulin pump. Alternatively, if the patient chooses to remain on injections until the next day, full transition back to insulin pump will take place the next day or after 22 h from the last glargine dose received at the hospital, and the patient will bolus for carbohydrates and correction with insulin injections. A similar approach can be used if the patient last received a glargine dose at bedtime the night before discharge.

Offering eligible patients, the option to continue with wearable technology while admitted to a hospital should be the main goal. At the University of California San Diego Health (UCSDH), a comprehensive computerized provider order entry set (CPOE) for insulin pump ordering is available via the electronic medical record platform. Eligible patients are required to sign the agreement for the use of their own insulin pump and/or CGM. It is an informed decision, and patients agree to BG POCT at a minimum before meals and at bedtime. CGM readings may assist with BG trending and alerts/alarms in the setting of glycemic variability (hyperglycemia and hypoglycemia). Patients are expected to keep a daily log and document glucose readings, bolus insulin doses (nutritional and correction), and insulin pump settings on their bedside documentation sheet. These forms are available in both English and Spanish to accommodate for patient demographics. Please refer to Chap. 7 “Insulin Pump Management in the Hospital” and to Chap. 8 “Use of CGM in the Inpatient Setting” for a detailed review of AID and CGM systems.

Perioperative Management and T1DM

In comparison to the general population, patients with T1DM are more likely to be at risk for increased morbidity and mortality, to be admitted for procedures that otherwise could be performed in the outpatient setting, to have an extended length of stay, and to have increased glycemic variability and increased risk for hypoglycemia due to periods of brief versus extended fasting [19].

Perioperatively, achieving and maintaining optimal inpatient glucose management in T1DM must account for multiple variables. It includes disease acuity (critically or non-critically ill), duration of procedure, level of consciousness, cognition, and ability to self-manage (if to remain on own insulin pump and/or CGM). Decisions are also leveraged by preoperative glycemic control (HbA1c or fructosamine) and insulin management format (i.e., MDI or CSII).

Foundationally, patients with T1DM must have their basal insulin replacement needs met uninterruptedly in order to stave off DKA. Seamlessly planning for vulnerable times is a must. For planned procedures, preoperative insulin adjustments ought to be made in anticipation of optimizing perioperative glucose management.

Anticipating challenges such as that presented by lengthy procedures would require the coordination between the outpatient and inpatient teams including the diabetes specialty team, anesthesiology, and pharmacy to readily transition from patient's own insulin pump to IV insulin drip or vice versa as needed without interruption in insulin delivery.

The Endocrine Society's 2022 guidelines for the management of hyperglycemia in hospitalized adults in noncritical care settings recommend that patients on insulin pumps prior to admission should remain on their devices instead of being switched to subcutaneous insulin regimen, granted that direct access to a diabetes specialty consult group is available. For those at high risk for hypoglycemia, the use of CGM along with confirmatory BG POCT is recommended. Carbohydrate-containing fluids preoperatively are discouraged. Carbohydrate counting with prandial insulin coverage using an insulin-to-carbohydrate ratio (I:CHO) or no carbohydrate counting using a fixed-insulin meal dosing with administration parameters is also recommended [33]. Further in-depth discussion surrounding perioperative type 1 DM management is found in Chap. 19.

Immunotherapy-Induced T1DM: Checkpoint Inhibitor-Related Autoimmune Diabetes Mellitus (CIADM)

Newer oncological immunotherapy with immune checkpoint inhibitors (ICIs) has become available for advanced cancer treatments. Along with these treatments came a novel, rare, typically irreversible, and fulminant, rapid-onset diabetes type known as CIADM, or also referred to as immune checkpoint inhibitor-associated diabetes mellitus (ICI-DM) [34, 35]. The sudden onset of CIADM reflects the fast decline in pancreatic beta cell function [34–36]. CIADM is a serious immune-related adverse event (irAE) secondary to the use of ICIs and is considered a life-threatening adverse event in which patients often present in severe diabetic ketoacidosis (DKA) and go on to need lifelong insulin replacement therapy [34–37].

CIADM develops in older adults undergoing immunotherapy for advanced cancers, in comparison to prototypical spontaneous/classical childhood T1DM. CIADM is marked by a rapid onset with DKA most commonly present, lower A1C levels due to short period of high blood glucose elevation prior to diagnosis (weeks to months), low or undetected C-peptide levels, antibodies present in about 50% of diagnosed patients [38], and honeymoon period not expected to be present. In prototypical spontaneous T1DM, antibodies are present in 90% of the children and adolescents, C-peptide levels are varied and slowly decrease, and there is a honeymoon period [16, 35].

It is paramount that guidelines aimed at mitigating the burden of CIADM in those who may be at a higher risk be developed and that patients be educated. Akturk and Michels recommend that healthcare providers in the process of selecting candidates for checkpoint inhibitor therapy screen for patients with preexisting

autoimmune disorders, autoantibodies, and HLA typing. Zhang et al. recommend that fasting or random plasma glucose as well as HbA1c levels be measured prior to and with each ICI administration [36]. Akturk and Michels recommend that HbA1c levels be monitored, self-monitoring of blood glucose be started, and use of CGM therapy be considered [35]. Wu et al. recommend that both oncologists and endocrinologists collaborate in setting glycemic targets for patients who undergo ICI therapy as goals of therapy may differ in the setting of survival outcomes, cancer prognosis, and comorbidities [34]. Tachibana et al. recommend that providers look for other endocrine irAEs such as thyroiditis, hypopituitarism, and adrenal insufficiency in patients with a new diagnosis of CIADM [37].

Until inpatient guidelines that address the management of CIADM become available, it is recommended that patients undergoing treatment with ICIs who present to the emergency room with overt signs and symptoms suggestive of hyperglycemic emergencies be ruled out for CIADM. If available, consulting with the endocrinology and diabetes specialty team is preferred. If a diagnosis is confirmed, a multidisciplinary team approach that also includes certified diabetes care and education specialists (CDCESs) and/or board-certified advanced diabetes management specialists (BC-ADMs) would be best suited to address patients' need to immerse in intensive CIADM management knowledge and skills training. It is also fundamental that these newly diagnosed patients with CIADM receive referrals to endocrinology and ideally leave the hospital with a scheduled appointment to ensure a seamless and timely transition of care to the outpatient setting.

Conclusion: On The Horizon—Present and Future Trends; Glucose Telemetry

In a very near future, as further accuracy and validation of wearable technology studies continue to be carried out in the inpatient setting and are granted FDA clearance, there will be a rise in demand for healthcare providers and staff education as the incorporation of glucose telemetry debuts and becomes embedded into the electronic health record allowing for remote monitoring and clinical decision support systems (CDSS). Please refer to Chap. 9 “Computer-Guided Approaches to Inpatient Insulin Management.”

Commercially available hybrid closed-loop AID systems continue to advance (Medtronic 670G and 780G, Tandem Control-IQ, CamAPS FX, Diabeloop, and Insulet's Omnipod 5). In the pipeline, dual-hormone systems (insulin and glucagon) and fully closed-loop system studies are underway [39] as well as inpatient AID system studies. An inpatient T1DM feasibility study with a Lilly automated insulin delivery (AID) system with a hybrid closed-loop pump along with embedded algorithm and CGM has shown appropriate responses to both meal and exercise challenges with increased glucose time in range (TIR) and no increase in hypoglycemia [40]. On the horizon lies the hope for the once-a-week basal insulin to soon become

a reality [41]. Weekly basal insulin dosing presents as a promising and ideal alternative especially for those with T1DM who experience recurrent DKA.

CGM technology for hospital glucose management will continue to evolve for both interstitial and intravascular monitoring; the future holds overcoming disparities in validity and reliability in the prevention and detection of hypoglycemia, compatibility with imaging studies, integration with AID system, medication interaction, and incorporation into hospital-wide glucose telemetry with expert oversight. Presently, challenges to overcome include CGM lag between interstitial and blood glucose level when levels rapidly shift such as in hypoglycemia or hyperglycemia and integrating CGM data with EMR. Additional factors such as implementation costs and training may also hinder the timely adoption of such therapies [13].

Streamlining inpatient workflow for the resolution of DKA may soon include the use of POCT bedside ketone testing meters. The recently released Joint British Diabetes Societies for Inpatient Care (JBDS-IP) guidelines for the management of diabetic ketoacidosis in adults provide the rationale for the use of capillary ketone testing monitors. In 2014, in the UK, about 76% of institutions had the capacity to use ketone POCT [42]. In a 10-year (2008–2018) retrospective pediatric Japanese study, serum 3-hydroxybutyrate (3HB) bedside measurements were suggested to be useful in establishing the time to DKA resolution (median of 10–11 h) in patients with T1DM without severe complications. Patients with monogenic diabetes, chronic liver disease, chronic renal disease, and heart failure were excluded [43].

In this not-so-distant future lies the hope for the safe and effective way to achieve and maintain euglycemia in the hospitalized patient with T1DM, thereby lessening the disease burden, morbidity, mortality, and associated direct and indirect costs of inpatient T1DM management [44]. As inpatient glycemic management research continues to advance and make strides towards the integration of CGM and AID systems, clinical decisions leveraged by EMR-integrated glucose telemetry will soon become the mainstay.

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Chapter 5

Diabetes in the Critically Ill Patient: DKA, HHS, and Beyond



Baani Singh, Sylvia Chlebek, and Armand Krikorian

Introduction

The American Diabetes Association (ADA) and the American Association of Clinical Endocrinology (AACE) define inpatient hyperglycemia as blood glucose >140 mg/dL [1, 2]. Hyperglycemia in critically ill patients has been associated with increased morbidity and mortality [3]. It can occur in the setting of preexisting type 1 or type 2 diabetes mellitus (DM) [4] or in patients with no prior diagnosis of diabetes [5]. In patients with a prior diagnosis of DM, hyperglycemia can occur as part of a crisis, such as diabetic ketoacidosis (DKA) [6] or hyperosmolar hyperglycemic state (HHS) [7] or as less acute, but still important, blood glucose elevation above optimal levels [8]. It is important to recognize that certain geographic locations and certain races have an unacceptably higher mortality rate in the setting of hyperglycemic crises [9]. These disparities may be due to differences in access to resources and healthcare, making an individualized and holistic approach to the management of hyperglycemia key to the appropriate care of the critically ill patient.

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Diabetic Ketoacidosis

Diabetic ketoacidosis (DKA) is characterized by the triad of hyperglycemia, metabolic acidosis, and hyperketonemia. Patients with type 1 DM are more prone to this metabolic emergency due to their lack of endogenous insulin production. It can also occur in a subset of patients with type 2 DM who may have ketosis-prone diabetes or been misdiagnosed as type 2 DM with a true diagnosis of latent autoimmune diabetes in adults (LADA) [10]. Another clinically significant variation of this metabolic emergency is euglycemic DKA (euDKA), which has been observed in DM patients on sodium glucose cotransporter-2 inhibitor (SGLT2i) therapy [11]. The approximate incidence of DKA was 55.5 cases per 1000 person years from 2007 to 2019 with an increase in the hospitalization rate in patients below the age of 45 [12, 13] and a decreased in-hospital mortality from 1.1 to 0.4% from 2003 to 2014 [14].

DKA Pathophysiology

DKA occurs due to an absolute insulin deficiency leading to an inability of cells to take up glucose and potassium—this leads to relative extracellular hyperglycemia and hyperkalemia with simultaneous intracellular deficiency of both. Insulin deficiency promotes ketonemia [7], and glucagon upregulation stimulates hepatic glycogenolysis and gluconeogenesis, further compounding the extracellular hyperglycemic hyperosmolarity [15–17]. This leads to osmotic diuresis and metabolic acidosis.

In euglycemic DKA (euDKA), a subtype of DKA, SGLT2 inhibitors' (SGLT2i) usage precipitates DKA. SGLT2i enhances the excretion and blocks reabsorption of glucose leading to a state of carbohydrate starvation and volume depletion, with the subsequent upregulation of glucagon leading to dehydration and ketosis in the absence of hyperglycemia [18, 19]. The effects of SGLT2i are independent of the duration of exposure, placing patients at risk of developing euglycemic DKA at any point during therapy [20, 21].

DKA Precipitating Factors

The precipitating factors for DKA and euDKA include any disease states that result in insulin deficiency. This includes acute infections, poor oral intake, low carbohydrate diet, cardiac events, stroke, pancreatitis, pregnancy, illicit substance abuse, and trauma. First-time diagnosis of type 1 diabetes and lack of access or adherence to insulin therapies are other common precipitants of DKA [22, 23].

DKA Clinical Features and Diagnostic Criteria

The diagnosis of DKA can be made through a combination of clinical signs and biochemical markers. Clinically, patients can present with polyuria, polydipsia, abdominal pain, nausea, vomiting, Kussmaul respirations, altered mental status, or severe dehydration [24]. The biochemical criteria to diagnose DKA include blood glucose >200 mg/dL; ketones positive in urine or beta-hydroxybutyrate >3 mmol/L; and venous pH <7.3 or bicarbonate <15 mEq/L, as well as the presence of a high anion gap (>12) metabolic acidosis [25]. Biochemical results can further stratify DKA into mild, moderate, or severe, determined by pH, bicarbonate, and mental status [4] as shown in Table 5.1.

DKA Management

Treatment protocols can vary slightly depending on the institution; however, the four tenets of DKA management are prompt identification and treatment of the precipitating cause, restoration of circulatory volume, clearance of ketones with insulin therapy, and correction of electrolyte imbalances. The management of DKA typically necessitates an intensive care setting, although some studies have suggested a possible role for less severe cases to be managed using subcutaneous insulin outside the ICU [26, 27]. Examples of protocols using subcutaneous insulin every 1–2 h for mild-to-moderate DKA management are outlined in Table 5.2. While the initial data seemed to suggest at least a non-inferiority of subcutaneous insulin use, a more recent systematic review found the evidence to be mostly of low quality [28]. A simpler but less studied approach used at some institutions when nursing policy only allows a maximum of every 4-h glucose monitoring outside of the ICU is to administer long-acting basal insulin (e.g., glargine) at 0.2 units/kg every 24 h along with a corrective scale of rapid-acting insulin every 4 h, coupled with nil per os (NPO) status and dextrose-containing intravenous fluids until biochemical resolution of DKA.

Table 5.1 Classification of severity of DKA

| | pH | Bicarbonate | Anion gap | Mental status |
|----------|-----------|-------------|-----------|------------------|
| Mild | 7.25–7.3 | 15–18 | >10 | Alert |
| Moderate | 7.00–7.24 | 10–15 | >12 | Mildly altered |
| Severe | <7.00 | <10 | >>12 | Severely altered |

(Adapted from Kitabchi et al. 2009)

Table 5.2 Protocols using subcutaneous rapid acting insulin (aspart or lispro) for mild-to-moderate DKA management

| | Umpierrez et al. (2004) q1h protocol | Umpierrez et al. (2004) q2h protocol | Della Manna (2005) q2h protocol | Karoli et al. (2011) q2h protocol |
|---------------------------|---|---|---|--|
| Glucose >250 mg/ dL | Initial dose of 0.3 units/kg body weight, followed by 0.1 units/kg every hour | Initial dose of 0.3 units/kg followed by 0.2 units/kg 1 h later and repeat every 2 h | Initial dose of 0.15 units/kg subcutaneously every 2 h | Initial bolus of 0.3 units/kg followed by 0.2 units/kg 1 h later and then 0.2 units/kg every 2 h |
| Glucose <250 mg/ dL | Insulin dose reduced to 0.05 units/kg every hour and the IV fluids were changed to D5% 0.45 | Insulin dose reduced to 0.1 units/kg every 2 h | Insulin dose reduced to 0.15 units/kg lispro insulin every 4 h for the next 24 h | Insulin dose reduced to 0.1 units/kg every 2 h |
| Goal glucose | 200 mg/dL | | | |

(Adapted from Andrade Castellanos et al. 2016)

Fluid Resuscitation and Restoration of Circulatory Volume

Current guidelines recommend the initial stratification of patients into two groups: mild-to-moderate dehydration versus severe dehydration with hemodynamic compromise [4]. In hemodynamically stable patients, the recommendation is to initiate 0.9% normal saline if hyponatremia is present and 0.45% normal saline if hypernatremia or normal serum sodium is present, with an initial rate of 15–20 mL/kg body weight per hour or 1–1.5 L during the first hour. The goal is the replacement of half of the total water loss over a period of 12–24 h [4, 22].

Electrolyte Imbalances

While patients typically present with hyperkalemia due to insulin deficiency, total potassium stores are usually deficient and will be further exacerbated by the intracellular movement of potassium with insulin therapy. Some protocols recommend addition of potassium to resuscitation fluids, while others replenish potassium on an as-needed basis based on lab findings. Regardless, frequent electrolyte monitoring and aggressive replacement are recommended to prevent cardiac arrhythmia or respiratory muscle weakness. The second consideration for frequent monitoring is acid–base status in severe DKA. At a pH >7, insulin can inhibit lipolysis and correct ketoacidosis. Bicarbonate use remains controversial with unclear benefit as it comes with adverse effects of hypokalemia, decreased oxygen uptake in peripheral tissues, and delay in ketosis resolution [4, 29].

Insulin Therapy

Insulin therapy is initiated once the serum potassium is >3.3 mmol/L. While various DKA insulin infusion protocols have been published, very little evidence exists evaluating their comparative effectiveness [30]. Most regular insulin infusion protocols are initiated at an initial rate of 0.1 units/kg/h. When the blood glucose reaches 200–250 mg/dL, dextrose-containing fluids are recommended. This combination is maintained until the anion gap resolves, which indicates resolution of ketoacidosis. The ADA criteria for resolution of DKA are glucose <200 mg/dL and two of the following criteria: serum bicarbonate >15 mEq/L, pH >7.3 , and anion gap <12 mEq/L. Once DKA has been resolved, clinically stable patients can be transitioned to an appropriate basal/bolus insulin regimen [2, 8, 25].

Transitioning from Insulin Infusion to Basal-Bolus Insulin Regimen

Transitioning to a basal-bolus regimen can be achieved by using one of the three approaches. The first approach is to resume the patient's pre-admission insulin regimen if deemed appropriate. The second approach, most appropriate for insulin-naïve patients, is to start a weight-based insulin regimen which can be determined by calculating a total daily insulin dose of 0.5–0.6 units/kg/day, with the total dose equally divided between basal and prandial insulin. The third approach attempts to estimate insulin requirements directly from the insulin infusion rate. This is done by calculating the average units per hour over a period when insulin requirements are stable and extrapolating to 24 h to calculate the estimated daily requirements of the patient (i.e., average drip rate over last 6 h \times 24 h/day). This number is then multiplied by 80% and distributed into 50% basal and 50% bolus doses. Regardless of which approach is used, the basal insulin should be administered 2 h prior to the discontinuation of the insulin infusion [2, 8, 25, 31].

Hyperosmolar Hyperglycemic State

Patients who are in hyperosmolar hyperglycemic state (HHS) will have severe hyperglycemia, profound dehydration, or altered consciousness. Patients with type 2 diabetes mellitus comprise 90–95% of HHS cases. HHS has an estimated mortality rate of 5–20%, which is significantly higher than the $<1\%$ mortality rate seen in DKA [9]. Obesity and carbohydrate-rich diet have led to an increase in the incidence of HHS because these conditions cause insulin resistance.

HHS Pathophysiology

In contrast to DKA, the presence of insulin prevents ketogenesis and lipolysis. While both HHS and DKA are insulin-deficient states, insulin deficiency in HHS is relative, with elevation of counterregulatory hormones such as glucagon, catecholamines, and cortisol ultimately leading to stimulation of glycogenolysis and gluconeogenesis [4]. While the insulin levels in HHS prevent or minimize the degree of lipolysis and ketogenesis, there is still significant hyperglycemia with resultant glycosuria, severe dehydration, and hyperosmolality.

HHS Precipitating Factors

HHS is commonly precipitated by an infection (50–60%) but can also be triggered by poor medication adherence, restricted water intake, or drugs such as beta-blockers, thiazides, glucocorticoids, and second-generation antipsychotic agents [32].

HHS Clinical Features and Diagnostic Criteria

Due to a lack of acidosis, HHS typically takes a slower course of symptom onset compared to DKA, with symptoms developing over several days. Patients experience a longer period of hyperglycemia-induced osmotic diuresis, and there is typically a larger water deficit in HHS (9 L) compared to DKA (6 L) [4]. In addition to polyuria, polydipsia, and generalized weakness, altered mental status is a classic finding in patients presenting with HHS [33]; seizures and transient hemiplegia have also been reported [34]. The presence of fever or leukocytosis greater than 25,000/ μ L may suggest an underlying infectious process [35]. The diagnostic criteria for HHS include severe hyperglycemia (>600 mg/dL), hyperosmolarity, near-normal pH (>7.3) and serum bicarbonate (>20 mEq/L), as well as near-absent serum and urine ketones [4]. The common diagnostic criteria that differentiate HHS from DKA are represented in Table 5.3 [4, 34].

Table 5.3 Diagnostic criteria for HHS versus DKA

| | Arterial pH | Plasma glucose (mg/dL) | Serum bicarbonate (mEq/L) | Anion gap | Serum osmolality | Ketones |
|-----|-------------|------------------------|---------------------------|-----------|------------------|---------------|
| HHS | >7.30 | >600 | >15 | <12 | >320 mOsm/kg | None or trace |
| DKA | ≤ 7.30 | >250 | <18 | >12 | Variable | Present |

(Adapted from Kitabchi A, et al. Diabetes Care, 2006, 29: 2739–2747)

Table 5.4 IV Fluid replacement in DKA and HHS

| | | | | |
|------------------|---------------------------------------|-------------------------------|------------------------------|---------------------------|
| Plasma glucose | Initial, >600 mg/dL | n/a | n/a | <250 mg/dL |
| Corrected sodium | n/a | >140 | <140 | n/a |
| IV Fluid choice | 1000 mL 0.9% NaCl bolus in first hour | 0.45% NaCl, rate 250–500 mL/h | 0.9% NaCl, rate 250–500 mL/h | D5 addition to NaCl fluid |

Table 5.5 Potassium repletion during DKA and HHS treatment

| | | | |
|------------------------|--------------------------------|--|------------|
| Potassium level | <3.3 mEq/L | 3.3–5.3 mEq/L | >5.3 mEq/L |
| Insulin infusion | Hold | Continue | Continue |
| IV Potassium repletion | 20–30 mEq/h until K >3.3 mEq/L | 20–30 mEq/L IV fluid to maintain K 4–5 mEq/L | Hold |

(Adapted from Kitabchi A, et al. Diabetes Care, 2006, 29: 2739–274)

HHS Management

Fluid Resuscitation and Restoration of Circulatory Volume

Similar to DKA, treatment of HHS includes aggressive fluid replacement with intravenous 0.9% saline solution, correction of hypokalemia, and intravenous insulin. One liter of IV 0.9% saline should be given in the first hour of diagnosis, followed by a continuous rate of 250–500 mL/h [4, 33] (Table 5.4). The rate of fluids should be adjusted based on hemodynamics, and a more conservative approach may be needed in patients at risk for fluid overload. For a corrected sodium less than 135 mEq/L, isotonic saline can be continued, whereas a normal or elevated sodium (greater than 140 mEq/L) should prompt the transition to 0.45% saline. Additionally, once the glucose level falls in the range of 250–300 mg/dL, 5% dextrose should be added to the IV fluids [33].

Electrolyte Management

Potassium repletion is the next important step in HHS management (Table 5.5). Serum potassium can be normal or elevated on initial presentation due to extracellular shifts in the setting of insulin deficiency and hyperosmolality. Similar to DKA, a serum potassium >3.3 mEq/L is needed prior to initiating insulin. Additionally, serum magnesium levels should also be monitored and repleted as necessary [36]. Electrolytes, BUN, creatine, plasma osmolality, and plasma glucose should be evaluated every 2–4 h until the patient is stable.

Table 5.6 IV Regular insulin infusion during DKA and HHS treatment

| Serum glucose level | Initial, >600 mg/dL | <300 mg/dL | <250 mg/dL |
|-----------------------|---|---------------------|---|
| Insulin infusion rate | Bolus 0.1 units/kg, then infusion of 0.1 units/kg/h; non-bolus 0.14 units/kg/h infusion | 0.05–0.1 units/kg/h | 0.05–0.1 units/kg/h, with addition of dextrose to IV fluids |

(Adapted from Kitabchi A, et al. Diabetes Care, 2006, 29: 2739–274)

Insulin Therapy and Transition to a Basal-Bolus Regimen

Following initial fluid and potassium correction, a continuous infusion of regular insulin should be initiated [4] (Table 5.6). An initial bolus of 0.1 units/kg body weight can be given followed by a continuous infusion of 0.1 units/kg/h. Alternatively, a continuous infusion of 0.14 units/kg/h can be initiated without an initial bolus. Capillary blood glucose levels should be monitored every hour to closely adjust the insulin infusion. When the plasma glucose reaches 300 mg/dL, the insulin infusion can be reduced to 0.05–0.1 units/kg/h. If the glucose falls below 250 mg/dL, the addition of dextrose to the IV fluids is important to maintain a level between 250 and 300 mg/dL until the patient's hyperosmolality and clinical condition improve. When the combination of plasma glucose <300 mg/dL and plasma osmolality <315 mOsm/L is achieved in an alert patient, subcutaneous insulin therapy can be initiated [4]. Similar to the transition protocol for DKA, there are three approaches to transitioning a patient to a basal-bolus regimen: resuming home dosage, weight-based calculations, or using insulin drip requirements. These are outlined in the “Transitioning from Insulin Drip to Basal-Bolus Insulin Regimen” section earlier in this chapter.

Treatment Considerations in Special Populations: CKD and Heart Failure

DKA/HHS management protocols often do not address special patient populations such as patients with chronic kidney disease (CKD) or congestive heart failure (CHF). In CKD patients, each tenet of DKA/HHS treatment is affected by impaired renal clearance and fluids; insulin as well as potassium must be carefully monitored and administered. While some data suggests worse outcomes in patients with both DKA and ESRD [37], there is little evidence on the appropriate therapeutic adjustments to initiate [38]. Insulin should be carefully managed due to the risk of hypoglycemia with aggressive treatment due to decreased renal clearance. Since physiologic diuresis is impaired due to CKD, fluids should be administered in smaller quantities with close monitoring to prevent complications such as pulmonary edema. Similarly, aggressive potassium replacement in CKD can result in

life-threatening hyperkalemia. Dialysis is recommended if hyperkalemia is intractable and associated with EKG changes.

There are also no specific guidelines to date on specific management of hyperglycemic emergencies in patients with heart failure [39]. Patients are often intravascularly depleted during the hyperglycemic state while appearing peripherally overloaded. The fluid status in patients with heart failure can be monitored via non-invasive or invasive methods. If there are signs of worsening hemodynamics, such as hypotension, cool extremities, or poor urine output, then this might warrant the use of vasoactive drugs and escalation of treatment to a critical care setting. As outlined above in the CKD section, challenges with fluid management and electrolyte abnormalities warrant a more conservative approach than the typical guidelines allow.

Hyperglycemia in the ICU

Besides DKA and HHS, hyperglycemia is a common occurrence in the critical setting, estimated to be present in up to 32% of patient-days [31]. While the trials from Leuven initially suggested tight blood glucose control in the ICU [40], data from the NICE-SUGAR trial [41] have resulted in a more optimal target of 140–180 mg/dL, a range adopted by the current recommendations from the American Diabetes Association and the American Association of Clinical Endocrinology [1, 2]. Studies have suggested that hyperglycemia in hospitalized patients is associated with worse outcomes, although that impact may be more pronounced in the absence of a prior diagnosis of diabetes mellitus [42]. Intravenous insulin remains the modality of choice in the ICU, in part due to its short half-life and in part due to the wide availability of different insulin infusion protocols [43]. These protocols either rely on human-initiated adjustments or can be computerized, with conflicting data on the superiority of one type vs. the other [44, 45]. More recently, a study involving 58 patients pointed to the potential of safely using subcutaneous insulin glargine in critically ill patients [46]. Insulin infusion protocols in the intensive care setting rely on frequent glucose monitoring using point-of-care testing with continuous glucose monitoring in the ICU still not FDA approved, although recent data from its use during the Covid-19 pandemic is encouraging [47].

Conclusion

DKA, HHS, and other hyperglycemic emergencies significantly contribute to morbidity and mortality in critically ill patients. While the pathophysiology of each hyperglycemic emergency is distinct, their treatment protocol is based on identifying the precipitating cause, fluid resuscitation, insulin administration, and correcting electrolyte abnormalities. The mainstay of treatment is usage of an insulin drip;

however, insulin de-escalation and fluid administration are individualized to each patient's unique metabolic profile. While the management can be complex, the goal is to bring the blood glucose to a range of 140–180 mg/dL. In patients with HF and CKD, it is recommended to use a conservative approach to fluid resuscitation and carefully monitor for signs of volume overload. Many cases of DKA and HHS can be prevented by improved access to medical care, awareness of socioeconomic determinants of health, and sick day management plans for patients with diabetes.

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Chapter 6

Use of Non-insulin Agents for Hyperglycemia Management in Hospitalized Patients



Yael T. Harris, David M. Reich, and Xiao Qing Li

Introduction

A substantial body of literature demonstrates the association between hyperglycemia in hospitalized patients—both with and without preexisting diabetes—and poor clinical outcomes (reviewed in [1]). Historically, clinical guidelines have recommended stopping oral agents and treating patients with basal-bolus insulin or intravenous insulin infusion during hospitalization [2–4], and insulin thus serves as the mainstay of glycemic management in hospitalized patients. However, insulin increases the risk of hypoglycemia. Accumulating data show the safety of newer non-insulin agents with low hypoglycemia risk, and recent professional society guidelines include consideration of some oral agents for specific populations [5, 6]. In this chapter, we discuss the evidence behind the use of non-insulin agents for inpatient glucose control.

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Metformin

Metformin is the most used oral hypoglycemic agent worldwide [7] and is the first-line treatment for most patients with type 2 diabetes mellitus (T2DM). It inhibits gluconeogenesis and lipogenesis in the liver and promotes glucose uptake and utilization in muscle cells. The affordability and low hypoglycemia risk of metformin make it an appealing choice for use in hospitalized patients, though concern exists regarding the rare but life-threatening possibility of metformin-induced lactic acidosis. The American Diabetes Association recommends against inpatient use of metformin due to the lack of randomized controlled trials (RCTs) on its safety and efficacy in hospitalized patients and the risk of lactic acidosis [8]. Nonetheless, data from US drug databases indicate that 25% of hospitalized patients with T2DM receive metformin [9].

While dangerous, the rate of metformin-associated lactic acidosis is extremely low. Estimates of its incidence range from 2 to 9 cases per 100,000 patient years [10, 11]. A 2010 Cochrane review of prospective trials and observational cohort studies found no difference in the level of lactate or risk of lactic acidosis between metformin and other non-metformin antihyperglycemic treatments [12]. Multiple studies show minimal lactic acidosis risk when metformin is used according to label, and that risk primarily occurs in the setting of renal insufficiency, severe liver dysfunction, decompensated heart failure, and overdose [13, 14].

In a single-center, retrospective cohort study, Alauddin et al. investigated the safety and efficacy of inpatient metformin use in non-critically ill adult patients with T2DM. Patients were divided into three groups, metformin only, metformin with oral diabetes medications, and metformin with insulin. Recommended inpatient glucose targets were achieved in all groups. Of the 200 patients identified, 55.5% had risk factors for developing lactic acidosis or contraindications to metformin use. There were no cases of lactic acidosis [15]. While this study demonstrates that metformin can safely help attain inpatient glycemic goals, the high rates of use in patients at risk of lactic acidosis raise serious concerns. Two other studies of inpatient metformin prescribing similarly found that >60% of patients prescribed metformin had risk factors for lactic acidosis [16, 17].

Recently, the use of metformin in patients hospitalized with COVID-19 has been evaluated. Surprisingly—given the risk of lactic acidosis with COVID-19—several small retrospective studies demonstrate decreased mortality in hospitalized patients with COVID-19 prescribed metformin. A retrospective cohort study of 131 patients with T2DM admitted for COVID-19 pneumonia found that patients on metformin during hospitalization had significant survival benefit compared to patients on insulin, sulfonylureas, or neither. The study found no significant difference in the mean baseline glucose between the groups [18]. A retrospective, single-center study in Brazil reported similar findings; patients with T2DM on metformin ($n = 115$) showed a significantly lower mortality (3.5%) than those not on metformin ($n = 73$; mortality 20.5%) [19]. A meta-analysis of nine studies evaluating mortality in patients hospitalized with COVID-19 and T2DM showed an association between

metformin use and lower mortality [20]. Metformin's anti-inflammatory effects may underlie this relationship. Its ability to decrease the downstream cellular pro-inflammatory markers while increasing the anti-inflammatory cytokines could ameliorate the cytokine storm associated with severe COVID infection [20]. While these results are hypothesis-generating, more data including prospective research are needed prior to recommending metformin use in this setting.

Professional societies recommend against metformin therapy in hospitalized patients due to lack of sufficient data; however, metformin continues to be widely used with minimal lactic acidosis. Given its substantial role in outpatient diabetes management and overall safety profile, RCTs are warranted to clarify the role of metformin in inpatient glycemic control. In the meantime, cautious use in select individuals without risk factors for lactic acidosis may be reasonable with continued monitoring and discontinuation of metformin if conditions predisposing to lactic acidosis develop.

Sulfonylureas

Sulfonylureas are among the oldest oral hypoglycemic agents available. They stimulate insulin release from pancreatic beta-cells in a glucose-independent manner, leading to an increased risk of hypoglycemia [21]. Multiple prediction models designed to identify patients at risk for inpatient hypoglycemia include sulfonylurea use as an element of risk [22, 23]. A retrospective cross-sectional analysis of 9584 diabetes admissions found that 20% of hospitalized patients treated with sulfonylureas experienced at least one episode of hypoglycemia [24]. Similarly, a nested case-control study at a single center in the USA demonstrated a hypoglycemia rate of 19% among hospitalized patients on sulfonylurea therapy [25]. In both studies, renal insufficiency and advanced age further increased hypoglycemia risk.

Sulfonylureas demonstrate neuroprotective properties in animal models of stroke, via blockade of neuronally expressed nonselective cation channels regulated by the sulfonylurea receptor 1 that cause cell death and cerebral edema under ischemic conditions [26]. While a retrospective study in humans indicated that sulfonylurea use prior to and during hospitalization for acute ischemic stroke correlated with improved patient outcome [27], subsequent studies [28, 29] found no difference in stroke severity or outcome. Since hypoglycemia is associated with increased morbidity and mortality in hospitalized patients [30], the risks of sulfonylurea use outweigh the potential benefits and they should be avoided in the hospital setting.

Thiazolidinediones, Meglitinides, Alpha-Glucosidase Inhibitors

Minimal data exist regarding the safety and efficacy of thiazolidinediones (TZDs), meglitinides, and alpha-glucosidase inhibitors in treating inpatient hyperglycemia. TZDs work as agonists of peroxisome proliferator-activated receptor gamma in adipocytes, stimulating adipogenesis and fatty acid uptake. They decrease insulin resistance in liver, muscle, and adipose tissue [31]. Data from a US hospital drug database demonstrated a 7% prevalence of use in hospitalized patients with T2DM [9]. In a small case-matched study of T2DM patients admitted for acute stroke rehabilitation, patients treated with TZDs showed improved functional recovery, with no difference in complications or length of stay. Data on glycemic control, hypoglycemia, and heart failure exacerbations were not reported [32]. While the potency and negligible risk of hypoglycemia with TZDs make them an attractive option, their impact on fluid retention raises concerns about the safety of inpatient use. Additionally, the ~2-week delay until effect on plasma glucose [33] makes initiation in the hospital impractical.

Meglitinides—short-acting insulin secretagogues—bind to ATP-dependent K⁺ channels on pancreatic beta-cells causing depolarization and increased insulin secretion. Despite their short duration of action, they can induce hypoglycemia, and prediction models for inpatient hypoglycemia include them as a risk factor [34, 35]. Alpha-glucosidase inhibitors block conversion of polysaccharides to monosaccharides, slowing carbohydrate absorption and decreasing postprandial hyperglycemia. They commonly cause gastrointestinal side effects, limiting their attraction for inpatient use.

Dipeptidyl Peptidase-4 Inhibitors

In contrast to the above agents, dipeptidyl peptidase-4 inhibitors (DPP-4-I) have substantial evidence supporting their safe and effective use for non-critically ill patients with mild-to-moderate hyperglycemia [36–41]. They produce minimal side effects [42], though saxagliptin and alogliptin can increase the risk of congestive heart failure [43, 44]. Inhibition of DPP-4 reduces the breakdown of the endogenous incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), stimulating insulin and inhibiting glucagon in a glucose-dependent manner, thereby decreasing glucose without the risk of hypoglycemia [42].

The Sita-Pilot trial [36] randomized 90 patients (55 medical, 35 surgical) to treatment with either sitagliptin, sitagliptin plus basal insulin, or basal-bolus insulin therapy without sitagliptin. Patients had admission blood glucose (BG) values of 140–400 mg/dL and outpatient regimens of either diet alone, oral diabetes medications, or ≤0.4 units/kg/day of insulin. There was no significant difference between the groups in mean daily BG level after 1 day of treatment and no significant

differences in the frequency of hypoglycemia. Of note, patients randomized to the sitagliptin-alone group with an initial serum glucose value above 180 mg/dL had a nonsignificantly higher mean daily BG level compared to patients treated with basal-bolus therapy and sitagliptin plus basal insulin therapy (182.7 ± 30 mg/dL vs. 168.1 ± 31 mg/dL vs. 161.8 ± 31 mg/dL, respectively, $P = 0.08$) [36].

In the Sita-Hospital trial [37], 277 adult patients with T2DM treated with either diet, oral diabetes medications, or insulin at ≤ 0.6 units/kg/day, with admission BG between 140 and 400 mg/dL, admitted to medicine (84% of patients) and surgery (16% of patients), were randomized to treatment with sitagliptin plus basal insulin or basal-bolus insulin. The mean daily BG in the sitagliptin plus basal insulin group was non-inferior to that in the basal-bolus insulin group. Rates of hypoglycemia did not differ significantly between the groups, nor did the length of hospital stay or frequency of the composite outcome of complications including infections, acute respiratory failure, acute kidney injury, reoperation, and myocardial infarction. This study excluded patients with clinically relevant hepatic disease and stage 4 or 5 chronic kidney disease.

Garg et al. randomized 66 patients with T2DM admitted to either medicine or surgery to receive saxagliptin or basal-bolus insulin in an open-label trial [38]. The mean BG on days 2–5 of hospitalization did not differ significantly between the groups. Continuous glucose monitoring data from 36 patients demonstrated a lower mean amplitude of glycemic excursion (MAGE), [i.e., the mean of blood glucose values exceeding one standard deviation (SD) from the 24-h mean blood glucose] and lower SD in the saxagliptin group compared to the basal-bolus insulin group, indicating lower glycemic variability [38].

In a multicenter RCT of patients admitted for elective noncardiac surgery, patients received linagliptin 5 mg daily or a basal-bolus insulin regimen [39]. While the mean daily BG was higher in the linagliptin group overall, among patients with BG < 200 mg/dL at randomization, mean daily BG during days 2–10 of hospital stay did not differ significantly between the groups. In patients with randomization BG ≥ 200 mg/dL, the linagliptin group had a higher average daily BG compared to patients in the basal-bolus group (196.2 ± 46.8 mg/dL vs. 165.6 ± 39.6 mg/dL, respectively, $P < 0.001$). Hypoglycemia occurred in fewer patients in the linagliptin group compared to the basal-bolus group with no difference in hospital complications [39].

In the Lina-Surg study [40], an observational, retrospective, multicenter study of T2DM patients admitted to noncardiac surgery units, treatment with a basal-bolus insulin regimen or a regimen of linagliptin and basal insulin resulted in equivalent mean BG levels after day one. Hypoglycemic events occurred significantly less frequently in the linagliptin plus basal group.

A recently published prospective randomized study evaluated the use of vildagliptin with basal insulin compared to basal-bolus insulin in 94 hospitalized patients aged ≥ 65 admitted to the medical service [41]. The mean HbA1c of the vildagliptin-basal group was $6.7 \pm 1.2\%$ and that of the basal-bolus group was $6.6 \pm 0.9\%$, $P = 0.85$. The mean BG did not differ significantly between the groups throughout the hospital stay. Hypoglycemia occurred in more patients in the basal-bolus group

compared with the vildagliptin-basal group. These results provide reassurance as to the safety and efficacy of DPP-4-I plus basal insulin therapy in elderly hospitalized patients. However, the relatively small sample size and a patient group with well-controlled diabetes may limit their generalizability to the broader population of elderly patients with T2DM.

In summary, several studies demonstrate the safety and efficacy of DPP-4-Is for treatment of non-critically ill hospitalized patients with type 2 diabetes mellitus [36–41]. Recent guidelines from the Endocrine Society and American Association of Clinical Endocrinology now include consideration of these agents in specific hospitalized patients [5, 6]. Data show that the use of a DPP-4-I with basal insulin and correctional rapid-acting insulin as needed produces equivalent glucose control compared to basal-bolus insulin. Various types of patients were generally excluded including those with severe hyperglycemia (serum glucose >400 mg/dL) on admission and with home insulin doses exceeding 0.6 units/kg of body weight/day. Some studies excluded patients on home insulin altogether [38, 40]. The data on DPP-4-I use in surgical studies included only patients undergoing elective surgery who were relatively well controlled at baseline [39, 40]. In patients with a HbA1c >9%, DPP-4-I therapy is less likely to control inpatient hyperglycemia, even together with basal insulin therapy [37].

Inpatient DPP-4-I use should thus be reserved for patients with mild-moderate hyperglycemia. In light of society guidelines and the above-reviewed literature, we recommend consideration for inpatient use of DPP-4-I for type 2 DM with HbA1c <8%, admission BG <180–200 mg/dL, and if using insulin prior to admission, total daily dose <0.6 units/kg/day [5, 6]. This applies both to patients using and not using DPP-4-I prior to admission. DPP-4-I may be used in combination with a correctional scale of rapid-acting insulin, or combined with basal insulin and correctional scale depending on the level of glucose. Patients with more significant hyperglycemia or those requiring basal and bolus insulin would not be recommended for inpatient use of DPP-4-I. Finally, it seems prudent to avoid saxagliptin or alogliptin in patients with a history of congestive heart failure.

Glucagon-Like Peptide-1 Receptor Agonists

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) activate GLP-1 receptors leading to enhanced glucose-dependent insulin release, decreased glucagon secretion, delayed gastric emptying, and increased satiety [42]. GLP-1 RAs effectively decrease HbA1c, produce weight loss, and reduce major cardiovascular events (reviewed in [45]). Clinical guidelines now include them as potential first-line agents for treatment of T2DM [6, 46], and their use in the outpatient setting has grown dramatically. The decrease in glucose excursions and low risk of hypoglycemia with GLP-1 RAs make them attractive options for inpatient use.

Several trials explore the use of GLP-1 or GLP-1 RAs for glycemic control in cardiac surgery patients [47–51]. In a pilot study, 20 patients undergoing CABG

were randomized to perioperative infusion of native GLP-1 versus standard therapy. The GLP-1 group had lower perioperative glucose ($p < 0.05$) and 45% lower insulin requirements and required less inotropes and vasopressors [47]. Kohl et al. randomized 77 patients requiring cardiopulmonary bypass to GLP-1 infusion or placebo in addition to a standard insulin protocol. Patients treated with GLP-1 had lower mean BG ($p = 0.015$), with no difference in hypoglycemia [48]. Lips et al. reported similar findings in a study comparing exenatide infusion to placebo plus standard perioperative insulin in elective cardiac surgery patients. Exenatide-treated patients had lower average BG ($p < 0.001$), greater time in target range ($p = 0.001$), and similar hypoglycemia rates [49]. Besch et al. randomly assigned 104 CABG patients to intravenous exenatide or insulin, with addition of insulin to exenatide if glucose remained above goal. They found no significant difference between groups in the time in target range or in the incidence of hypoglycemia or nausea. The exenatide group required less insulin ($p < 0.001$) [50]. Likewise, in an RCT of 278 cardiac surgery patients comparing preoperative subcutaneous liraglutide in two escalating doses to placebo, fewer patients in the liraglutide group required addition of insulin ($p = 0.003$), with lower mean BG ($p < 0.001$). Hypoglycemia rates and nausea/vomiting did not differ between groups [51].

Perioperative GLP-1 and GLP-1 RA use has also shown benefit in noncardiac surgery patients. In a pilot crossover study, Meier et al. randomized eight patients with T2DM who had undergone major surgery to an intravenous infusion of GLP-1 followed by placebo or vice versa. Glucose values decreased to the normoglycemic range within 150 min with IV GLP-1 and not with placebo ($p < 0.001$) [52]. In an RCT, Polderman et al. compared preoperative subcutaneous liraglutide (0.6 mg the night prior and 1.2 mg the morning of surgery) to perioperative intravenous insulin infusion or basal insulin at 50% of the baseline dose in 150 patients scheduled for noncardiac surgery. Patients who received liraglutide had significantly lower glucose values 1 h postoperatively ($p = 0.015$) and lower total insulin requirements during the perioperative period ($p < 0.001$). They also experienced more nausea ($p = 0.007$). Hypoglycemia did not differ between groups [53].

Additional studies evaluated GLP-1-RA use in patients admitted to medical-surgical units. A small pilot study of liraglutide vs. basal bolus insulin [54] and a retrospective study comparing patients treated with vs. without dulaglutide [55] showed lower insulin requirements in GLP-1-treated patients. Larger prospective trials show improved glucose control with GLP-1 RAs. Fayfman et al. randomized 150 non-critically ill patients with T2DM to subcutaneous exenatide, exenatide + basal insulin, or basal bolus insulin. Patients in the exenatide + basal group had a greater percent of glucose values in target range (70–180 mg/dL) than either exenatide or basal-bolus groups (78% vs. 62% vs. 63%, respectively, $P = 0.023$). Exenatide-treated patients had higher rates of nausea than those on insulin only. Hypoglycemia and length-of-stay did not differ between groups [56]. Fushimi et al. compared basal and correctional insulin to dulaglutide 0.75 mg and basal and correctional insulin in 54 non-critically ill patients with T2DM. Dulaglutide-treated patients spent more time in the target range of 100–180 mg/dL (56% vs. 44%, $P < 0.001$). Mean BG, coefficient of variation, correctional insulin doses, and

hypoglycemia were significantly lower in the dulaglutide group, with similar rates of gastrointestinal symptoms [57].

In a trial exploring liraglutide use in critically ill patients, 120 patients admitted to an ICU with BG 181–300 mg/dL were randomized to insulin or liraglutide, for BG 181–240 mg/dL, and to insulin or insulin plus liraglutide, for BG 241–300 mg/dL. Similar proportions of patients in each group achieved the primary outcome of BG <180 mg/dL after 24 h. Patients on liraglutide had more gastrointestinal effects and less hypoglycemia than those on insulin [58].

In summary, studies thus far indicate that GLP-1-RA use in hospitalized patients can help achieve glycemic control with lower risk of hypoglycemia, though gastrointestinal side effects as well as cost represent limiting factors. Larger RCTs comparing long-acting GLP-1 RAs with insulin therapy could help elucidate this matter.

Sodium Glucose Co-transporter-2 Inhibitors

The sodium-glucose co-transporter 2 inhibitors (SGLT-2-Is) lower serum glucose by inhibiting the reabsorption of glucose in the proximal convoluted tubules of the kidney, leading to increased excretion of glucose in the urine [59]. Several RCTs using SGLT-2-Is have demonstrated significant reductions in cardiovascular and renal events in T2DM patients who are either at high risk for or have established cardiovascular disease. The most robust finding is a reduction in the risk of hospitalization for heart failure (reviewed in [60]).

Given the cardiac and renal benefits, the low risk of hypoglycemia, and the once-daily dosing, SGLT-2-I use in the hospital has garnered considerable interest. However, side effects include urinary tract and genital mycotic infections, dehydration, hypotension, and rarely Fournier's gangrene [61], limiting their potential inpatient use. Most concerning, SGLT-2-Is can precipitate diabetic ketoacidosis (DKA) [62], often with serum glucose values <250 mg/dL termed "euglycemic DKA," particularly in the setting of fasting or surgery [62]. Other risk factors for euglycemic DKA include reduction in insulin dose, ketogenic diet, hypovolemia, concurrent illness, and alcohol use [62]. The FDA has warned that SGLT-2 inhibitors should be stopped 3 days before scheduled surgery or other major procedures, such as a colonoscopy (4 days in the case of ertugliflozin) [63]. Data supporting the safe and effective use of SGLT-2-Is in the hospital setting is limited to date.

DARE-19 (Dapagliflozin in Respiratory Failure in Patients with COVID-19) was a randomized, placebo-controlled, double-blind trial of 1250 patients hospitalized with COVID-19 who had at least one cardiometabolic risk factor. Treatment included either 10 mg dapagliflozin or placebo for 30 days. Although fewer patients treated with dapagliflozin had organ failure or died, the differences did not reach statistical significance. Patients tolerated dapagliflozin well, and no new safety signals emerged. Only two cases of DKA occurred among the 625 patients receiving dapagliflozin, both in patients with T2DM, and resolved quickly with treatment [64].

The EMPA-RESPONSE-AHF study, a randomized, controlled, double-blind, multicenter pilot study, randomized 80 patients with acute heart failure (AHF) to empagliflozin or placebo for 30 days [65]. The empagliflozin group had a reduction in the combined endpoint of in-hospital worsening of heart failure, rehospitalization for heart failure, or death at 60 days compared to placebo (10% vs. 33%, $p = 0.014$). Rates of adverse events, including worsening renal function and urinary tract infections, did not differ between groups. Only one patient with T2DM developed DKA in the placebo group, and none in the empagliflozin group. However, only 15 patients with T2DM received empagliflozin and only 11 received placebo [65].

The SOLOIST-WHF trial, a double-blind, randomized, placebo-controlled trial in patients with T2DM hospitalized for heart failure, compared sotagliflozin—an SGLT-2-I that also inhibits SGLT-1 sites in the gastrointestinal tract—to placebo before or within 3 days after hospital discharge and followed patients for a median of 9 months. The primary endpoint was the total number of deaths from cardiovascular causes, and urgent visits and hospitalizations for heart failure. The sotagliflozin group had a lower number and rate of primary endpoint events compared to the placebo group. The incidence of death from cardiovascular causes or from any cause did not differ significantly between groups, nor did the rates of DKA [66].

The EMPULSE trial, a randomized, double-blind, placebo-controlled, multicenter trial, assessed the clinical benefit and safety of empagliflozin compared with placebo in 530 patients hospitalized with AHF and followed for 90 days post-randomization [67]. 46.8% of patients randomized to empagliflozin and 43.8% of patients randomized to placebo had T2DM. In the empagliflozin group, significantly fewer patients died and had at least one heart failure event. No episodes of diabetic ketoacidosis occurred in either the empagliflozin or the placebo group [67].

The ongoing DICTATE-AHF trial will provide more information. This prospective, multicenter, open-label, randomized trial intends to enroll 240 patients across the USA with T2DM and at most stage 3b chronic kidney disease, hospitalized for hypervolemic AHF. Patients will be randomized within the first 24 h to dapagliflozin 10 mg daily or structured usual heart failure care until day 5 or hospital discharge. The primary endpoint is diuretic response. Safety endpoints include the incidence of hyper/hypoglycemia, DKA, and mortality [68].

The American Diabetes Association recommends against routine inpatient SGLT-2-I use pending further data on safety and efficacy [8]. For hemodynamically stable patients with AHF and no risk factors for DKA, one could consider initiating an SGLT-2-I, particularly close to discharge, if precautions exist to ensure safe use and discontinuation when necessary. Appropriate patients include those tolerating a diet, with no planned procedures or periods of fasting in the next 3–4 days and no alcohol abuse, on adequate doses of insulin. For patients taking SGLT-2-Is who require unanticipated procedures or periods of fasting, the medication should be stopped immediately with assessment for DKA via basic metabolic panel, anion gap, venous pH, and serum ketones and with repeat testing post-procedure or during prolonged fasting [69]. Urinary ketones may not be reliable because SGLT-2-Is increase urinary ketone

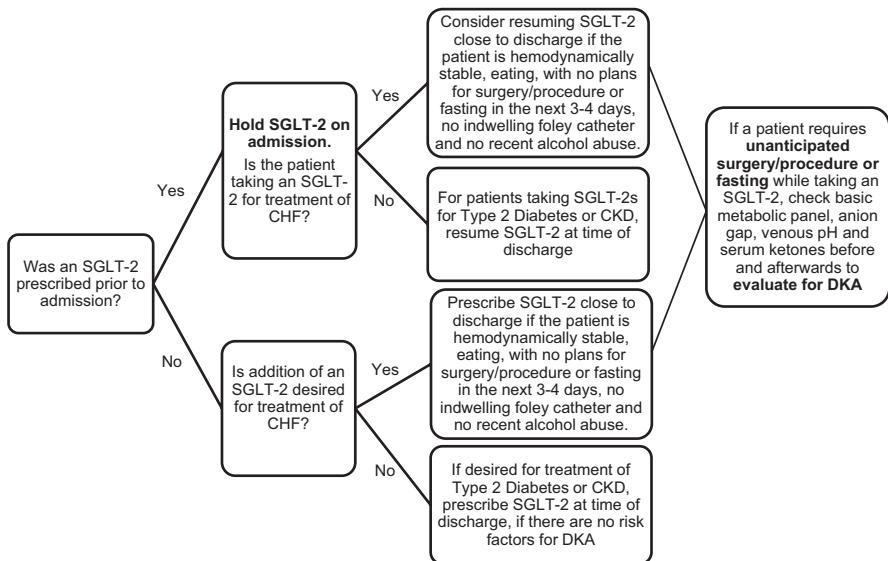


Fig. 6.1 Decision flow chart for inpatient use of sodium-glucose co-transporter 2 inhibitors to minimize the risk of diabetic ketoacidosis. *SGLT-2* sodium-glucose co-transporter 2 inhibitor, *CHF* congestive heart failure, *CKD* chronic kidney disease, *DKA* diabetic ketoacidosis

reabsorption [62]. Resumption of SGLT-2-Is should occur only after patients can tolerate a full diet. Figure 6.1 depicts a decision flow diagram on the use of SGLT-2 inhibitors in the hospital.

Conclusion

The management of inpatient hyperglycemia is undergoing a paradigm shift away from the notion that all patients need insulin. In particular, recent studies demonstrate that DPP-4-Is or DPP-4-Is with basal insulin can safely and effectively treat mild-to-moderate hyperglycemia. Data on GLP-1-RAs also appear encouraging, though insufficient as yet to recommend use. SGLT-2-Is may play a role in patients with congestive heart failure but would need safeguards implemented to prevent inappropriate use and avoid DKA. Finally, metformin deserves further study with randomized controlled trials as it likely represents a safe and inexpensive option for patients without risk factors for lactic acidosis (Fig. 6.2).

| Inpatient use of hypoglycemic agents | | | | |
|--------------------------------------|---|--|---|--|
| | | Advantages | Disadvantages | Consider for patients with: |
| Recommended | Basal-Bolus Insulin | <ul style="list-style-type: none"> Safe and effective based on RCTs in wide range of patients | <ul style="list-style-type: none"> Hypoglycemia risk Expensive | <ul style="list-style-type: none"> Admission glucose > 300 mg/dL HbA1c > 9% Insulin Resistance or multiple agents On steroids |
| | Dipeptidyl Peptidase-4 Inhibitor | <ul style="list-style-type: none"> Safe and Effective for mild to moderate hyperglycemia with low insulin requirements based on RCTs Low hypoglycemia risk | <ul style="list-style-type: none"> Not recommended for admission glucose > 300 mg/dL or insulin dose > 0.6 units/kg/day Expensive | <ul style="list-style-type: none"> Admission glucose < 200 mg/dL Admission glucose 200-299 mg/dL with basal insulin High risk of hypoglycemia No pancreatic disease |
| Consider | Metformin | <ul style="list-style-type: none"> Low hypoglycemia risk Low cost | <ul style="list-style-type: none"> Risk of lactic acidosis Contraindicated for GFR < 30 mL/min/1.73m² No RCTs | <ul style="list-style-type: none"> High risk of hypoglycemia On metformin preadmission No CKD or AKI, sepsis, severe CHF, or other lactic acidosis risk |
| | Glucagon-like Peptide-1 Receptor Agonist | <ul style="list-style-type: none"> Small trials show efficacy Low hypoglycemia risk | <ul style="list-style-type: none"> Gastrointestinal side effects Expensive | <ul style="list-style-type: none"> On GLP-1 preadmission No pancreatic disease |
| Not Recommended | Sodium Glucose Co-Transporter-2 Inhibitor | <ul style="list-style-type: none"> Beneficial in acute heart failure | <ul style="list-style-type: none"> Risk of DKA particularly with fasting or surgery Expensive No RCTs for glycemic control | <ul style="list-style-type: none"> CHF, close to discharge Consistent food intake No planned surgery or procedures Do not use in Type 1 Diabetes |
| | Sulfonylurea | | <ul style="list-style-type: none"> Substantial hypoglycemia risk Inpatient use not recommended | |
| | Thiazolidinedione | <ul style="list-style-type: none"> Low hypoglycemia risk | <ul style="list-style-type: none"> Risk of fluid retention Delayed onset of effect Minimal inpatient data | |
| | Meglitinide | <ul style="list-style-type: none"> Short acting | <ul style="list-style-type: none"> Risk of hypoglycemia (though less than for sulfonylureas) Minimal inpatient data | |
| | Alpha-glucosidase inhibitor | <ul style="list-style-type: none"> Targets post-prandial hyperglycemia | <ul style="list-style-type: none"> Gastrointestinal side effects No inpatient data | |

Fig. 6.2 Considerations for choice of hypoglycemic agents for inpatient glucose control. *RCT* randomized controlled trial, *GFR* glomerular filtration rate, *CKD* chronic kidney disease, *AKI* acute kidney injury, *CHF* congestive heart failure, *GLP-1* glucagon-like peptide-1 receptor agonists, *DKA* diabetic ketoacidosis

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Part II

Diabetes Technology in the Hospital

Chapter 7

Clinical Practice Update: Inpatient Insulin Pump and Integrated Insulin Delivery Systems



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Background

DM Prevalence

The prevalence of diabetes mellitus (DM) continues to increase at alarming rates nationally, with an estimated prevalence of 11.3% of the US adult population [1]. More than 130 million adults have been diagnosed as having either DM or prediabetes. Approximately 283,000 children and adolescents have been diagnosed with DM. In total, approximately three million children and adults are estimated to have type 1 DM with steadily increasing incidence rates [1]. Globally, approximately 537 million adults are diagnosed with DM, and this is expected to rise to 643 million by 2030 [2].

Inpatient Glycemic Management

Concurrent with increased DM prevalence, there is an increase in hospitalizations among patients with DM, with 8.25 million US hospitalizations for adult patients with DM [1] and threefold higher rates of hospitalization among patients with type 1 DM when compared to the general population [3–5]. Inpatient DM management

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relies on subcutaneous insulin administration to achieve glycemic control. Insulin administration varies from the use of intravenous infusion in critical care settings to subcutaneous insulin regimens in the general ward settings. Basal-bolus insulin regimens have been effective in improving glycemic control and have been associated with lower risks of hospital complications [6, 7]. Yet despite improved management of inpatient hyperglycemia, glycemic control targets remain difficult to achieve with iatrogenic hypoglycemia being the most common complication of subcutaneous inpatient insulin therapy. Inpatient hypoglycemia has been associated with increased morbidity and mortality, increased length of stay, increased readmission rates, and increased cost burden [8–11].

Insulin Pump Therapy and Device-Driven DM Care

The use of devices to support or augment medication and lifestyle management for DM has been coined the term “device-driven DM care.” Over the past two decades, device-driven DM care has markedly increased in the ambulatory care setting in patients with type 1 and type 2 DM [12]. Continued advances in continuous subcutaneous insulin infusion (CSII) systems, continuous glucose monitoring (CGM) systems, and automated insulin dosing (AID) systems have demonstrated benefit to both glycemic control and reduction in hypoglycemia compared to the use of multiple daily injections (MDIs) in both pediatric and adult populations [12–19]. Diabetes technology not only improves glycemic control metrics but has also been shown to improve the quality of life for patients in the ambulatory setting [20, 21]. Device-driven DM therapy has revolutionized the approach to outpatient DM care for many patients with type 1 and type 2 DM with rapid advancements intended to mimic physiologic insulin secretion. Prior to 1990, less than 7000 US insulin pump users were reported [22]. As of 2011, an estimated 400,000 patients with DM in the USA were identified as insulin pump users [23–25]. According to recent Type 1 Diabetes Exchange updates from 2016 to 2018, approximately 63% of individuals with type 1 DM in the USA use insulin pumps [26–28]. Historically, primarily patients with type 1 DM were initiated on insulin pump systems. However, a steadily increasing number of patients with type 2 DM are now transitioning to insulin pump therapy [29]. The wide phenotypic variability of patients with type 2 DM presents challenges in combining non-insulin agents with device-driven DM care. Yet, there is emerging evidence of the benefits of CSII and AID systems in patients with type 2 DM [30, 31]. One large study explored the impact of CSII versus MDI in 495 patients with uncontrolled type 2 DM. At 6 months, the mean HbA1C decreased by 1.1% in the insulin pump therapy group as compared to 0.4% in the MDI group. This reduction was achieved despite a lower total daily insulin requirement in the CSII group [32]. A study of 40 inpatients with type 2 DM were randomly assigned to either closed-loop intervention group or control group receiving standard of care. The target glucose range was defined as 100–180 mg/dL for up to 72 h. The proportion of time spent in the target range was significantly greater in the intervention

versus control, demonstrating the safety and efficacy of closed-loop insulin delivery among inpatients with type 2 DM [33, 34].

Evolution in Insulin Pump and CGM Systems

Conventional Insulin Pump Therapy

Understanding the evolution in device-driven DM care provides a framework for recognizing the risks and benefits of currently used FDA-approved insulin pump and sensor systems. Historically, insulin pump delivery systems were considered as a stand-alone therapy. However, in the past two decades, the integration of CGM and advancements in insulin delivery algorithms has resulted in dynamic systems using smart technology. A stand-alone insulin pump is a device that delivers a continuous infusion of insulin through a cannula inserted directly into the subcutaneous tissue. The cannula connects either directly to the reservoir as is used in tubeless devices or to a plastic tubing or infusion set, as is used in tubed devices. Rapid-acting and regular insulins are the current FDA-approved insulins for patients treated with an insulin pump. This method of insulin pump therapy has been termed continuous subcutaneous insulin infusion (CSII) [35].

In CSII, there are two settings for insulin delivery—basal and bolus settings. The basal setting replaces long-acting insulin, and the rates of infusion are based on shared decision-making between patient and specialist. A personalized basal rate is created to optimize glycemic control primarily in a fasted state. Patients are educated on the unique benefits of temporary basal settings that can deliver a reduced or increased percentage, based on the clinical needs of the patient. The temporary features are intended to be used by the patient on an as-needed basis. For example, a patient may be counseled to initiate a 50% temporary basal prior to vigorous exercise for hypoglycemia prevention. Conversely, in patients receiving steroid regimens, a temporary basal may be increased for several hours after steroid administration to compensate for the anticipated steroid-induced hyperglycemic trends (e.g., 120% or 140%). A temporary basal rate of 80% is sometimes used for patients nil per os (NPO) past midnight for procedures.

The bolus settings provide the patient with guidance in the management of prandial insulin delivery and corrective actions for hyperglycemia management. The patient enters carbohydrates and/or blood glucose values into the bolus menu, and based on the settings that are entered by the specialist, the pump will provide recommendations for bolus insulin delivery. Bolus settings include insulin-to-carbohydrate ratio, insulin sensitivity factor, blood glucose target, and active insulin time. Certain pumps may have extended bolus options, also known as dual-wave bolus or combination bolus, that permit a percentage of the recommended bolus to be delivered up front, and the remaining percentage to be delivered over a preferred interval of time. The creation of these unique features in the original insulin pumps helped patients

adapt to each unique circumstance and metabolic requirement. For example, a patient with gastroparesis may require 25% of the recommended bolus to be delivered up front and the remaining 75% of the recommended bolus to be delivered slowly over the remaining 2–3 h. Patients are advised that food combinations with higher fat content may require extended bolus insulin delivery to compensate for the expected longer postprandial hyperglycemic excursions. Patients are recommended to undergo extensive nutritional counseling, to demonstrate proficiency in carbohydrate counting, and recognize the importance and adherence to routine premeal glucose monitoring. These behaviors play an integral role in bolus dosing.

Sensor-Augmented Insulin Pump (SAP)

In 1999, the first CGM device was released by the FDA. These devices measure glucose concentration in the interstitial space between 1 and 15 min apart and provide trends in overall glycemia. Devices were created for both professional use in the clinic setting and personal use. With the release of “real-time” CGM devices that also provide alarms for low and high sensor values, a new role for CGM emerged in the integration of CGM with insulin pump therapy, called sensor-augmented insulin pump (SAP). The insulin pump screen serves as a receiver for CGM data and can be tied into the insulin pump algorithm. A growing body of literature revealed the unique benefits of SAP in significantly reducing HbA1C while avoiding hypoglycemia, as compared to patients on MDI when followed for 12 months. The STAR3 study revealed that children and adolescents were more likely to achieve recommended glycemic targets on SAP as compared to MDI with reduced glycemic variability [36]. Thereafter, accelerated advancements in device technology quickly resulted in SAP combined with low glucose sensor “threshold suspend” delivery systems affording a 40–50% reduction in hypoglycemia without an increase in A1C [37, 38]. This was shortly followed by “predictive threshold-suspend” systems that additionally permitted a 50–80% reduction in nighttime hypoglycemia and a 31–50% reduction in hypoglycemia when compared to SAP alone [39–42].

Automated Insulin Dosing (AID) Systems

Tremendous strides in DM technology up until the point of predictive low glucose suspend technologies focused primarily on hypoglycemia prevention while achieving recommended HbA1C targets. However, novel CGMS metrics revealed persistence of glycemic variability and unique ability to report overall glycemic control in terms of the percent of time that sensor values were measured within pre-specified ranges (<70 mg/dL, 70–180 mg/dL, and >180 mg/dL). Additionally, despite the benefits of suspend features for hypoglycemia prevention, there were still periods of unchecked hyperglycemia. Automated insulin dosing (AID) systems further

improved glycemic control by providing dynamic sensor-driven insulin dosing adjustments in the form of micro-bolus or auto-correction on a minute-to-minute basis. These delivery systems are driven by a control algorithm that calculates and dynamically adjusts insulin delivery, either in a predictive fashion or in a threshold-driven programming [43–47]. Recent advancements include the bionic pancreas (insulin-only type), demonstrating superiority in glycemic control when compared to “standard care” including all other forms of insulin delivery, without the requirement for insulin pump settings or carbohydrate counting. As this is a novel technology that is imminently emerging in clinical practice, additional investigation is warranted to assess effectiveness in the inpatient setting [48].

Insulin Pump Transitions into the Inpatient Setting

Increased use of DM devices in the outpatient setting is paralleled by an increased trend for continuation of patient-directed DM self-care technologies in the inpatient setting.

Recent endocrinology guidelines support continued CSII, SAP, AID, and CGM systems in clinically appropriate inpatients [49–52]. The use of stand-alone CGM therapy in the inpatient setting is discussed in Chap. 8 [49–52]. Prior studies have reported non-inferiority of CSII to subcutaneous injections and increased patient satisfaction when permitted to continue DM self-care in concert with inpatient protocols [53]. In one large study of 136 patients, spanning 253 hospitalizations, CSII was continued for 65% of hospitalizations. Mean glucose was not significantly different among patients who remained on CSII as compared to those for whom it was discontinued. Additionally, episodes of hyperglycemia (>300 mg/dL) and hypoglycemia (<40 mg/dL) were significantly fewer in CSII therapy users [54]. It is imperative that hospital-based healthcare providers and nursing staff understand and feel comfortable with managing DM devices under the guidance of DM specialists. Here, we review current approaches to consideration and continuation of DM technology systems in the inpatient setting. As there are several combinations of insulin delivery and CGM options currently available, we will refer to stand-alone insulin pump delivery as continuous subcutaneous insulin infusion (CSII) and integrated insulin pump and CGM devices, as sensor-augmented insulin pump (SAP) therapy, or automated insulin dosing (AID) systems.

Ideal Insulin Pump Candidates in the Inpatient Setting

Consensus Guidelines and Updates

Several professional organizations including the Endocrine Society, the American Association of Clinical Endocrinology, the American Diabetes Association, the Association of Diabetes Care and Education Specialists, and the American College

of Endocrinology have issued consensus guidelines regarding inpatient insulin pump therapy [29]. The guidelines support continuation of insulin pump therapy in patients who are deemed clinically appropriate candidates under the guidance of endocrinology or DM specialists. Such patients should demonstrate mental, physical, and cognitive capabilities for self-directed DM care and should be willing to adhere to the inpatient hospital protocols, policies, and procedures [29].

The 2017 consensus statement was updated in 2020 to include the use of automated insulin dosing (AID) systems [55]. The expert panel reviewed the medical literature on the use of CGM and AID systems in the inpatient setting and provided three forms of recommendations (clinical practice, research, and hospital policies) that were then classified as either strong or mild. The experts conclude that recommendations are intended to provide evidence-based guidance for safe and effective implementation of CGM, CSII, and AID systems in the inpatient setting, a reliable resource for clinicians, researchers, manufacturers, and hospital systems [55].

The American Diabetes Association and the American Association of Clinical Endocrinology support continuation of insulin pump therapy in the inpatient setting under the current circumstances: (1) Patients demonstrate cognitive, emotional, and physical capabilities to continue insulin pump therapy. (2) There is a hospital policy in practice for CSII use that includes involvement of DM or endocrinology specialists with expertise in insulin pump and CGM technologies. (3) Clear policies and procedures should be established and made available for review by the patient continuing CSII therapy as well as all hospital staff involved in the care of the patient. (4) Clear documentation of insulin pump settings (basal rates, bolus insulin calculations including insulin-to-carbohydrate ratio, insulin sensitivity factor, active insulin time, blood glucose target), dietary recommendations, and recommended frequency of glucose measurements should be made available to the healthcare team. (5) A signed patient agreement should include all the above policies, procedures, expectations of the patient and healthcare team, and the patient's consent to adhere to these recommendations and report any issues to the healthcare team in a timely manner [29, 56–59].

Clinical Indications

The criteria to initiate pump therapy outpatient have a different focus compared to the decision on continuation of insulin pump therapy inpatient. Based on consensus guidelines, there are several clinical indications to consider when initiating insulin pump therapy in the ambulatory care setting [35]. These indications or behavioral attributes include patients who are not meeting recommended glycemic targets, who are experiencing frequent hypoglycemia, nocturnal hypoglycemia, a history of hypoglycemic unawareness, or patients with a robust dawn phenomenon [60–62]. Other clinical considerations include

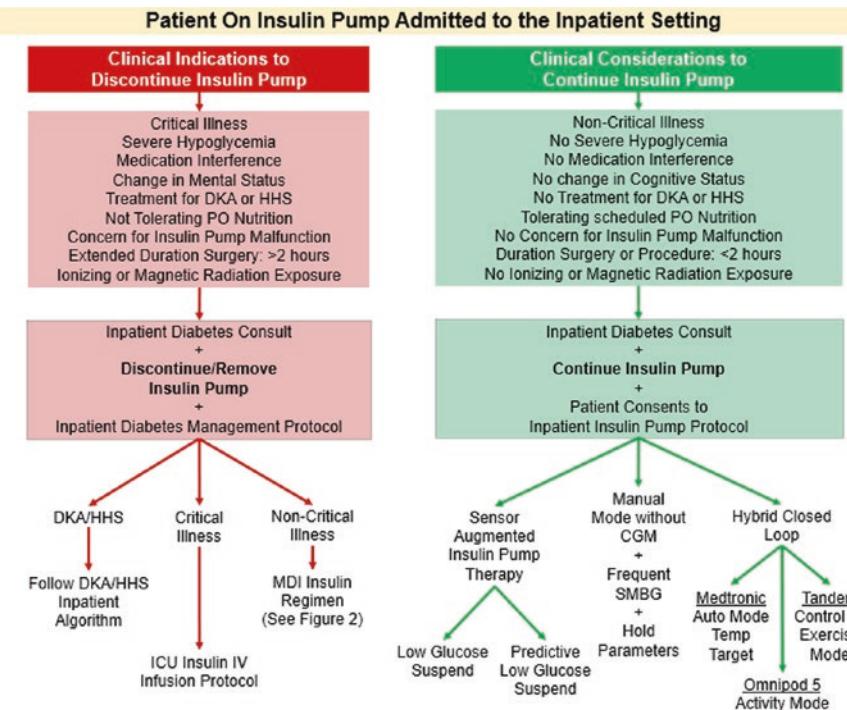


Fig. 7.1 This figure delineates clinical indications to discontinue insulin pump therapy (in red) and clinical considerations to continue insulin pump therapy (in green) in the inpatient setting. Ref: Umpierrez GE et al. Diabetes Care 2018; 41(8):1579–89. Doi: 10.2337/dc18-0002. *DKA* diabetic ketoacidosis, *HHS* hyperglycemic hyperosmolar syndrome, *PO* per oral, *MDI* multiple daily injection, *CGM* continuous glucose monitoring

patients experiencing gastroparesis, unpredictable eating habits, those requiring very small doses of insulin as in the pediatric population, or patients seeking a reduction in injection burden [35].

When a patient on an insulin pump system is admitted to the inpatient setting, it is reasonable to continue insulin pump therapy, if specific clinical criteria are present (Fig. 7.1). Continuation of therapy can be considered for patients undergoing surgical procedures with expected duration of 2 h or less. (Please refer to Chap. 19 Perioperative Management of Blood Glucose in Adults with Diabetes Mellitus in this book.) Continuation of therapy can also be considered for patients in the following context: (1) admitted to medicine or surgical ward setting, in a non-critically ill condition; (2) not receiving treatment for diabetic ketoacidosis; (3) able to operate the insulin pump with physical, mental, and cognitive faculties intact; (4) are agreeable to inpatient hospital policies and procedures; and (5) presence of consultant support by endocrinology or inpatient DM specialty care team (Fig. 7.1) [55].

Logistical Considerations

To safely continue CSII or AID therapy in the inpatient setting, several hospital-based tasks, roles, and responsibilities should be clearly delineated. Healthcare providers should review hospital policy and require the patient to sign an agreement indicating acknowledgment of this discussion. Healthcare providers should intermittently reassess whether the patient remains capable of DM self-management. Nursing staff should be informed of the signed policy and continue the standardized approach to documentation of glucose trends and insulin dose adjustments. The nursing staff should have access to the patient's daily sensor glucose trends, self-obtained capillary glucose values, and insulin bolus and basal rates. Furthermore, the patient should be agreeable to abide by hospital guidelines, which may also require the nursing staff to perform their standard point-of-care glucose testing. Specialty consultation is recommended for any inpatient that is permitted to continue CSII or AID therapy and should guide the primary team and nursing staff through any adjustments to the system as required [55, 63].

Behavioral Attributes

As DM technology advances and with the expansion of automated insulin dosing devices and smart technologies, there may be a concern that human behavior and patient-directed self-care strategies may be substantially reduced. The counterargument to this notion was aptly explained by O'Donell et al.: "even the most advanced technology can only be as effective as the person who uses it" [28].

Approach to Inpatient Management of Insulin Pump Therapy

Inpatient Endocrinology or DM Specialist Consultation

Often the patient may have greater proficiency in CSII than the nursing or healthcare provider staff, who may have little to no experience with managing DM devices. Successful use of CSII therapy requires collaboration among the patient, healthcare providers, and all ancillary hospital staff. Ideally, an inpatient hospital policy and computerized order set mitigates potential errors in interpretation and provides concise guidance to nursing. The primary team should consult endocrinology or inpatient DM specialists with proficiency in management of DM devices for all patients who remain on CSII or AID therapy. If a facility does not have endocrinology or DM specialists present, then consensus guidelines recommend a virtual consult for guidance. More research is warranted to delineate safe CSII or AID continuation for patients in remote or rural areas with limited access to specialty consultation services.

Adjusted Glucose Targets in the Inpatient Setting

Generally, recommendations for glycemic goals in the noncritical inpatient setting are to maintain glucose values between 100 and 180 mg/dL [64]. Adjustments to blood glucose target may be warranted to reflect this adjusted glycemic goal. This is particularly relevant in patients with acute kidney injury, with reduced nutrient consumption, or who may be at a higher risk for hypoglycemia. Any adjustments to pump settings should be clearly documented in the patient's chart and shared with all nursing and healthcare staff involved in the patient's care [53].

Patient Agreement with Inpatient Hospital Policies and Contract

Once the consultant service has deemed that a patient meets all criteria to continue insulin pump therapy, the patient should be informed about inpatient hospital policies and procedures regarding continuation of CSII or AID systems, express agreement to adhere to institutional policy, and sign a detailed contract. This contract should then become part of the patient's inpatient medical record [53].

Daily Data Review and Documentation

The patient should permit hospital staff to undergo a daily intake of the device and all components. Inspection should include extraction of data from the CSII and CGM system directly or remotely. The consultant team may also request the patient to provide written documentation of self-obtained sensor and capillary glucose values and cross-reference these values with nursing point-of-care glucose values. Efforts to ensure transparency in reporting ensures that the patient's safety is maintained as a priority while continuing CSII or AID systems [53].

Changing Pump Supplies and Refilling the Reservoir

Patients may not have prepared for inpatient admission and may not have access to all required insulin pump supplies. Continuation of CSII hinges on access to all required supplies. If possible, procuring supplies from the inpatient pharmacy or affiliated outpatient pharmacy is ideal, but may not always be possible. If the patient or a family member can obtain outpatient supplies, then CSII may be continued. If the patient must change the reservoir and insulin, it is generally advised that the patient receive insulin from the inpatient pharmacy, as this is deemed safer than using insulin that may have been brought from the outpatient setting [53]. Overall,

if the patient is unable to obtain any of their supplies, then transition to basal-bolus subcutaneous insulin regimen should be recommended.

Capillary Glucose Measurements and Insulin Dose Adjustments

Although patients may rely on sensor glucose trends and may even choose to monitor capillary glucose with their personal glucometer, the consultant team should reiterate the requirement of nursing point-of-care glucose testing that should be relied on for insulin dose adjustments and CGM calibration. Inpatient glucometers that are calibrated per inpatient hospital standards ensure accuracy in reported glucose values and impact the adjustments to CSII settings. Employing special features in AID systems such as temporary basal or automated settings may help to achieve recommended glycemic targets. However, consultant teams may choose to disable automated features and revert to manual modes for AID systems in the inpatient setting, while continuing threshold features that protect patients from impending hypoglycemia. The patient may be encouraged to include documentation of bolus insulin doses administered with sensor and capillary glucose measurements [53].

Physical Exam of Patient with Insulin Pump and CGM

Patients who are permitted to continue CSII or AID systems in the inpatient setting should agree to undergo daily physical exams. The exam includes inspection of the insertion site of both infusion set or tubeless pump insertion and CGM insertion. Documentation of the exam should include the presence or absence of signs of inflammation or infection at the site. It is recommended that pump site examination should be documented at least once every 48–72 h in the patient's chart. The date of last site change and the date of next anticipated site change can be documented in nursing notes and inpatient provider progress notes. Removal of CSII or CGM should also be documented as part of the physical examination [53]. These safety inspections can be done by a nurse and/or inpatient provider.

Diagnostic procedures using ionizing radiation, fluoroscopy, or magnetic resonance imaging can damage the pump and may require insulin pump and/or CGM removal. Insulin pump therapy may be continued during ultrasound and procedures such as colonoscopy and endoscopy. Depending on the location of the pump and CGM, the inpatient team may deem it safe to continue insulin pump and CGM for patients undergoing X-ray, CT scan, or cardiac catheterization, if the devices can be covered by a lead apron. However, this decision should be made on a case-by-case basis. Devices will need to be removed prior to MRI [53].

The consultant team should be involved in the coordination of DM care when any part of the CSII or AID system is removed and ensure that alternative insulin treatment options are provided during these periods of time. Safeguarding the

patient's pump and CGM is crucial as the healthcare teams may not be aware of which parts of the system are considered durable medical equipment (pump and transmitter) versus disposable pieces (infusion set, reservoir, and sensor). The consultant team should counsel the patient and nursing staff to identify a safe method of storing CSII and AID systems when not in use [53].

Cybersecurity and Hospital Policies

As technology advances and the use of smart, interactive devices expands, there is a growing concern for cybersecurity when using automated insulin delivery systems that communicate through cloud-based or wireless systems. The consensus agreement is that the comfort level of the institution should be gauged first when considering inpatient CSII or AID therapy [53].

Considerations to Continue or Discontinue CSII or AID Systems

Patients permitted to continue CSII or AID therapy during inpatient admission should demonstrate proficiency in several aspects of DM self-management. The patient should be able to deliver a bolus insulin dose, adhere to CGM and capillary blood glucose monitoring, demonstrate an appropriate level of manual dexterity in handling the pump and all required supplies, and be agreeable to changing the infusion set and reservoir at least once every 72 h or sooner as needed. If the patient does not demonstrate these proficiencies, then the DM specialty team may deem it appropriate to discontinue pump therapy during the inpatient setting [55, 65, 66]. These attributes are summarized in Fig. 7.1 [35]. Upon admission, the healthcare team and patient should deliberate carefully on the decision to continue insulin pump therapy on an individual basis. There are several factors that may preclude a patient from continuing CSII or AID systems upon admission. These factors are categorized as (1) patient related, (2) hospital related, (3) device related, (4) medication and nutrition related, and (5) surgical related.

Patient-Related Considerations to Continue or Discontinue CSII or AID

The reasons for inpatient hospitalization are varied from acute and critical illness to elective medical or surgical treatments. Patients admitted with severe metabolic compromise are at risk for tissue hypoperfusion. Examples include sepsis, volume depletion, adrenal insufficiency, acute kidney injury, diabetic ketoacidosis, and hyperosmotic hyperglycemia. For patients in diabetic ketoacidosis while on an

insulin pump, it would be necessary to transition them off the pump upon presentation until the cause of the diabetic ketoacidosis can be corrected or clarified regardless of the severity of the diabetic ketoacidosis (even if mild DKA and not overtly critically ill). If a patient is admitted directly to the intensive care unit in critical condition, then the patient is unlikely to have the physical, cognitive, or mental capabilities for DM self-management. Patients with extreme concentrations of thyroid hormone may predispose to hypoglycemia. Patients with acute alcoholic intoxication are also at risk for severe hypoglycemia and changes in mental status (Fig. 7.1) [67].

Patients presenting with acute skin disorders may prevent optimal placement of infusion set and tubing and may also pose a potential nidus for worsening infection. Skin irritation at the site of insertion is a common occurrence in pump users and may pose a challenge for consistent adherence to infusion set placement in the inpatient setting [68]. In such circumstances, the healthcare team may recommend discontinuation of CSII or AID systems and initiate standard inpatient subcutaneous or intravenous insulin therapy per hospital policy and protocol [55].

Hospital-Related Considerations to Continue or Discontinue CSII or AID

Hospital policies ideally should include a standard operating procedure that details a multidisciplinary approach for the continuation of CSII or AID systems. This hospital policy should delineate the goals and expectations of both the patient and the healthcare team. There are several circumstances that should be considered including adequate nursing training and support and presence of DM specialists with a proficiency in managing and interpreting the DM device data. The presence of an accepted hospital protocol protects the patient and the healthcare team. If such a protocol does not exist, it is best to discontinue CSII or AID systems and default to accepted inpatient DM care practices [55].

Device-Related Considerations to Continue or Discontinue CSII or AID

There are circumstances that may preclude continuation of CSII and AID systems due to device-related factors. There should be extensive education at the time of insulin pump initiation regarding the potential failures of the device and clear instructions should be received when they revert to multiple daily-injection regimen until clear guidance can be provided by the DM specialty team. This education is crucial for patients to understand device-related factors that may predispose to DM complications, such as diabetic ketoacidosis or severe glycemic excursions. If a

patient's history does not reveal a clear explanation for the extreme glycemic trends, then the patient and healthcare team may raise the question of CSII or AID system failure as a potential trigger for the event.

Potential failures for insulin delivery through CSII or AID systems include insulin pump malfunction, mechanical challenges such as twisted external tubing or bent cannula in the subcutaneous tissue, or denatured insulin in the reservoir itself. Patients using CGM as part of an AID system may position the sensor insertion in areas of dependency that becomes a challenge in the inpatient setting. Compression of the sensor can predispose to falsely low readings. The low alarms may set off a cascade of reactions from both patient and the nursing and healthcare teams, correcting a reported low sensor glucose prior to confirmation with a capillary glucose value. This may result in undue hyperglycemia. Therefore, when there is a concern that the device itself may be malfunctioning or the circumstances in the inpatient setting predispose to erroneous sensor glucose readings, the healthcare team may consider discontinuing CSII or AID systems and transition to standard inpatient DM management protocols [55, 69–71].

Medication and Nutrition-Related Considerations to Continue or Discontinue CSII or AID

There are several inpatient medication regimens that may predispose to either worsening hyperglycemia or increased risk for hypoglycemia. High-dose or prolonged steroid therapies worsen insulin resistance and increase the degree and duration of postprandial hyperglycemia. The calculated estimates for insulin-to-carb ratio and sensitivity factors may not adequately control for the effect of steroids and may require adjustments by the DM specialty team [72].

Conversely, there are several medications that may predispose to hypoglycemia including quinolones, trimethoprim-sulfamethoxazole, and beta-blockers. Additionally, patients with type 2 DM may also be concurrently treated with oral antihyperglycemic agents that may predispose to hypoglycemia. In such cases, the healthcare team may choose to hold CSII or AID systems until the high-risk medication is no longer required. If the new medication continues indefinitely, then insulin pump settings may need to be adjusted prior to discharge.

Additionally, CGM systems have various medication-related interferences, depending on the device and the drug. Some of these medications, including acetaminophen, aspirin, and hydroxyurea, may be used in the inpatient setting. These erroneous sensor glucose values can create confusion when interpreting sensor data as part of an AID system. The risk for potential drug interference related to sensor glucose accuracy may justify discontinuing an AID system during hospitalization.

Commonly, during inpatient admissions, the patient's nutritional status changes. Due to acute illness, patients may have symptoms such as nausea or vomiting that

preclude enteral feeding. This results in variable nutrient absorption and unpredictable glucose trends. Dietary orders may be held in preparation for radiographic studies or procedures [29]. Such circumstances pose challenges to consistent patient self-management of DM. Therefore, CSII and AID systems may be continued in the inpatient setting if the patient's nutritional status is expected to be relatively constant. However, in patients who require frequent imaging or procedures causing variability in their nutrition schedule, discontinuation of CSII or AID systems would be the safer option (Fig. 7.1) [72].

Surgical Related Considerations to Continue or Discontinue CSII or AID

Patients undergoing surgical procedures present a unique challenge for continuation of CSII or AID systems. Once an insulin pump is suspended, rapid-acting insulin is typically cleared within 2–4 h. Suspending an insulin pump without providing subcutaneous insulin coverage prior to a procedure that is anticipated to be 2 or more hours may increase the risk of diabetic ketoacidosis or uncontrolled hyperglycemia. Therefore, consensus recommendations indicate that if a procedure is expected to be greater than 2 h in duration, then it is safest to make the transition to standard subcutaneous or intravenous inpatient insulin protocols.

Emergent/urgent cases warrant prompt discontinuation of insulin pump and resumption of standard inpatient DM protocols as there is no data on the safe handling of AID systems in the intraoperative setting or the expectation that anesthesiologists would have the proficiency or specialty expertise in interpreting CGM and insulin delivery data or adjusting insulin pump setting.

Patients undergoing elective procedures less than 2 h in duration may be permitted to continue CSII or AID systems under the guidance of the inpatient DM specialty team. If such a specialty team is not present, then even in these instances, CSII or AID may be discontinued and the patient started on standard inpatient DM management protocols. Due to the lingering effects of anesthesia, patients may lack full cognitive function in the postoperative setting. Care should be taken when deciding to resume CSII or AID, and the guidance by the DM specialty team should be warranted [29, 53, 54].

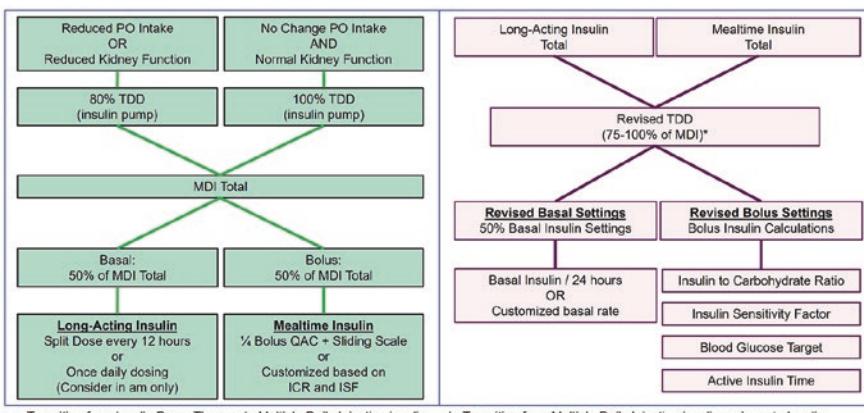
Hybrid closed-loop (HCL) systems allow for dynamic basal adjustments and may also include auto-bolus corrections. A preliminary case series recently reported that continuation of HCL technology may also be considered a viable option in the inpatient setting. With the adoption of clear institutional protocols, HCL can achieve comparable glycemic control, when compared to patients who used manual insulin pump therapy or who were transitioned to subcutaneous insulin regimen. Additionally, use of HCL can also improve patient satisfaction and reduce nursing workload.

Transitions Between Insulin Pump and Subcutaneous Regimen (See Fig. 7.2)

Transition from Insulin Pump to Subcutaneous Multiple Daily-Injection (MDI) Insulin Regimen

At the time of admission, if the admitting team deems it is safer to discontinue insulin pump therapy and initiate multiple daily-injection (MDI) insulin therapy, then following a few steps permits a smooth transition to safe and comparable MDI regimen. First, assess whether the patient has reduced kidney function, such as in patients with acute kidney injury or progression in chronic kidney disease. Such patients may be predisposed to hypoglycemia, due to reduced insulin clearance. Secondly assess whether the patient has reduced per oral (PO) intake. Lack of consistent meals or reduced consumption may also predispose patients to hypoglycemia. If either of these clinical conditions are present, then it is safer to reduce the estimated total daily dose (TDD) of insulin for conversion to MDI regimen. A suggested reduction is 80% of the patient's total daily dose, which can easily be obtained from the insulin pump settings or upon review of the patient's ambulatory glucose profile. If the patient is anticipated to have no change in PO intake and has normal kidney function, then it is reasonable to use 100% TDD for conversion to MDI. Please make note of the difference between total daily basal insulin and total daily dose, which includes both basal and bolus components.

Upon estimation of the MDI total, 50% can be allotted to basal insulin dosing. Ensure that basal insulin is initiated approximately 2 h prior to discontinuation of the insulin pump. This is particularly important for patients with insulinopenic DM, such as patients with type 1 or type 3C DM or patients with ketosis-prone DM. One



a. Transition from Insulin Pump Therapy to Multiple Daily Injection insulin regimen at the time of admission. TDD=total daily dose, MDI=multiple daily injection. QAC=with meals; ICR=Insulin to Carbohydrate Ratio; ISF=Insulin Sensitivity Factor

b. Transition from Multiple Daily Injection insulin regimen to Insulin Pump Therapy at the time of discharge to the ambulatory care setting.
*=revised TDD based on response to MDI regimen and clinical characteristics at the time of discharge.

Fig. 7.2 The figure illustrates the steps recommended when transitioning: (a) from insulin pump to multiple daily-injection regimen at the time of admission and (b) from multiple daily-injection regimen to insulin pump therapy at the time of discharge from the inpatient setting

common approach to basal insulin dosing in the inpatient setting is to split the dose, delivering half of the basal insulin every 12 h. This approach provides the inpatient team with a greater facility to make basal dose adjustments on a day-to-day basis and can expedite insulin dose titration to achieve recommended glycemic targets. However, the decision to split the dose of basal insulin should be considered on a case-by-case basis. If delivering basal insulin once daily, consider morning dosing. This permits the inpatient team to adjust the basal insulin dose and observe the intended changes in a proactive fashion. Once daily basal dosing at bedtime is another frequently used option, it may work well or even be preferred depending on the nursing and provider workflow (i.e., if rounds occur after the morning insulin would have already been administered).

The remaining MDI total can be allotted to mealtime insulin. A suggested approach is to calculate the patient's insulin requirement based on the carbohydrate content of the prescribed diet, taking into account the patient's carbohydrate ratio. Another approach is to estimate one-fourth of the mealtime total for each meal and add a correctional scale. The correctional scale can be customized according to the patient's calculated sensitivity factor or can be adjusted to the closest inpatient insulin sliding scale (Fig. 7.2).

Transition from Multiple Daily Injection (MDI) Insulin to Insulin Pump Therapy

As the patient approaches discharge, the inpatient teams may need to consider a revision in the insulin pump settings. Clinical factors that may warrant a revision in the insulin pump settings include changes in weight, renal function, or medication profiles. Considering all relevant clinical factors and the patient's inpatient subcutaneous insulin requirements can aid in the transition back to insulin pump therapy. Alternatively, if insulin requirements in the inpatient setting were only transiently reduced, related to reduced PO intake, and are expected to be normalized at discharge, then adjustment of home settings may not be required in some cases.

A suggested approach if adjusting home pump settings is to use 75% of the patient's inpatient subcutaneous MDI total. This calculation may be an underestimation of the patient's insulin requirements but offers a safe transition back to insulin pump therapy. Approximately 50% of the revised total daily dose is then allotted to basal insulin and can be divided by 24 h in a day. Alternatively, if the patient already has customized preset basal insulin settings, then the rates can be adjusted to reflect the new basal insulin requirement.

Bolus insulin settings can be revised using the new TDD to calculate the insulin-to-carbohydrate ratio and insulin sensitivity factor. If hypoglycemia is a greater concern at the time of discharge, then a higher blood glucose target may be considered. If the patient is using a hybrid closed-loop (HCL) system, the active insulin time may be fixed or adjustable, depending on the type of device and algorithm in use. In

general, a longer active insulin time results in a lower risk of hypoglycemia. An active insulin time of 4 h is suggested when using rapid-acting insulin in the insulin pump.

As the patient nears discharge, the timing of transition to insulin pump therapy is equally important as the revision in insulin pump settings. The first step is to determine when the last dose of long-acting insulin was administered. The pump should be restarted nearing the end of the long-acting insulin's full effect, approximately 18–22 h from the last dose of basal insulin. The team should then communicate with the patient, admitting team, and nursing staff at least 24 h prior to the recommended date and time for insulin pump restart. This allows the patient to collect all insulin pump supplies, gives time to nursing staff to procure rapid-acting insulin for reservoir fill, and ensures that estimates for revised insulin pump settings are communicated to the primary team. Diabetes education can also be provided nearing discharge, particularly if the settings have changed, and can also include giving the patient important contact information for insulin pump trainers and DM specialty staff. Finally, the patient should be counseled to make a follow-up appointment with his or her DM clinic provider in the ambulatory care setting for close outpatient follow-up after discharge. For patients using CGM either in parallel with insulin pump therapy or integrated, as in HCL systems, the sensor alarms may need to be adjusted according to the patient's clinical circumstance. Please see Chap. 8 dedicated to CGM in the inpatient setting for comprehensive guidance (Fig. 7.2).

Conclusion

In conclusion, this chapter provides a practical guide for the inpatient management of patients with DM on insulin pumps and/or continuous glucose monitoring systems. When considering continuation of insulin pump or integrated insulin delivery systems in the inpatient setting, the provider must deliberate on a myriad of factors that affect successful glycemic control, including the cognitive and clinical status of the patient, the device proficiencies of both patient and provider team, the willingness of the patient to adhere to inpatient protocols, the presence of a multidisciplinary team that specifically includes experts in device-driven DM care, and the presence of recommended hospital administrative policies and procedures. In the ideal clinical setting, treatment with inpatient insulin pump or integrated insulin delivery systems, in accordance with current standards of inpatient DM care, is a successful DM treatment strategy that prioritizes patient safety, hypoglycemia prevention, and stable glycemic control. Disclosures and Conflicts of Interest M. Vasudevan: no disclosures or conflicts of interest; S. Nguyen: no disclosures or conflicts of interest; G Davis: GMD is supported by the National Institutes of Health (NIH) under Award Number K23DK122199 and has received research support from Insulet Corp. and consulting fees from Medscape, Inc.

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Chapter 8

Continuous Glucose Monitoring in the Hospital Setting: Current Status and Future Directions



Georgia M. Davis and Madhuri M. Vasudevan

Introduction

Advancing diabetes technology has influenced outpatient diabetes management and impacted glycemic control metrics and quality-of-life measures for people living with diabetes over the past two decades [1–3]. This technology includes not only continued development of continuous glucose monitoring (CGM), continuous subcutaneous insulin infusion (CSII), and integration of these technologies into automated insulin delivery (AID) or artificial pancreas (AP) systems, but also advances in remote monitoring and data management systems [4]. Despite the growth of technology in the outpatient setting, inpatient use of diabetes technology remains limited mainly to research protocols or the continuation of a patient's personal devices during hospitalization. However, the coronavirus disease 2019 (COVID-19) pandemic necessitated new care management strategies for hospitalized patients with diabetes that could help reduce the use of personal protective equipment (PPE) leading to an unprecedented increase in the use of technology in the hospital setting, particularly CGM [5–9].

Interest in the use of subcutaneous CGM for management of hospitalized patients with diabetes is long-standing [10]. CGM employs a small flexible sensor inserted subcutaneously that measures interstitial glucose values every several minutes, providing estimates of blood glucose values and glycemic trends. The information obtained from the sensor is transmitted to a dedicated remote monitoring device or

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personal smartphone for visualization of sensor glucose data, which can be shared with remote viewers via cloud-based programs. Current commercially available subcutaneous CGM systems have improved accuracy and usability compared to earlier devices, with several factory-calibrated options that no longer require intermittent calibration with finger-stick glucose values (Table 8.1). Several of these current devices have received approval for non-adjunctive use in the outpatient setting, meaning that clinical decisions may be made using the sensor glucose value without a confirmatory finger-stick glucose. Compared to point-of-care (POC) glucose testing, CGM provides a more comprehensive picture of glycemic control data and trends, with newer devices measuring glucose values every 1–5 min [11]. Data on inpatient CGM use prior to the COVID-19 pandemic came from mostly smaller studies in both critical and noncritical care settings [10]. These studies focused predominantly on accuracy and glycemic control metrics with very limited data on clinical outcomes. Although the United States Food and Drug Administration (FDA) has not approved CGM for use in the hospital, they issued a statement of non-objection to CGM use for necessary care during the COVID-19 pandemic. This led to emerging data on CGM functionality in diverse patient populations across many different healthcare systems [6].

Hospital use of CGM provides not only the ability to closely monitor glucose values, but also the ability to do so remotely. This was particularly valuable during the pandemic with respect to PPE conservation and limiting healthcare provider exposures without compromising the frequency of glucose monitoring [5, 6, 9]. CGM-generated glycemic control metrics are also available for remote viewing, providing additional summary data on glucose trends and patterns to assist with clinical decision-making. Here, we review the current evidence on CGM use in the hospital setting, explore potential future uses, and discuss implementation needs as current research continues to examine the performance and application of CGM in diverse inpatient clinical scenarios.

Table 8.1 Current commercially available CGM devices

| | Abbott FreeStyle Libre 2 | Abbott FreeStyle Libre 3 | Dexcom G6 | Dexcom G7 | Medtronic guardian 3 | Medtronic guardian 4 | Eversense E3 |
|--------------------------------|--------------------------|--------------------------|-----------|-----------|----------------------|----------------------|--------------|
| Sensor warm-up time (h) | 1 | 1 | 2 | 0.5 | 2 | 2 | 24 |
| Required calibrations | – | – | – | – | ✓ | – | ✓ |
| Alarms and alerts | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Duration of sensor wear (days) | 14 | 14 | 10 | 10 | 7 | 7 | 180 |
| Remote sharing capabilities | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |

CGM in Noncritical Care Settings

Many studies on CGM use in the noncritical care setting have focused on assessing CGM accuracy and glycemic control during hospitalization. Prior to the emergent implementation of CGM with remote monitoring for clinical care during COVID-19 (Fig. 8.1) [8], use of CGM in the inpatient setting had remained purely investigational. A pooled analysis of CGM trial data was performed to provide further information on the reliability of CGM in different clinical scenarios and populations during the pandemic [12]. This study, examining the Dexcom G6 real-time CGM device, showed a mean absolute relative difference (MARD) of 12.8% between paired CGM and finger-stick glucose values with 98.7% of paired values falling within Clarke error grid zones A and B, supporting the reliability of CGM use in non-critically ill patients. However, reduced CGM accuracy was observed for CGM glucose values in the hypoglycemic range, during the first 12–24 h of sensor wear and in patients with severe anemia. To address previous concerns regarding sustained CGM accuracy surrounding radiology procedures and imaging modalities, Migdal et al. investigated CGM accuracy metrics prior to and following radiology procedures (excluding magnetic resonance imaging) with the Dexcom G6 CGM [13]. Overall, they reported no significant difference in CGM reliability after computed tomography, radiography, or angiography in 49 hospitalized patients.

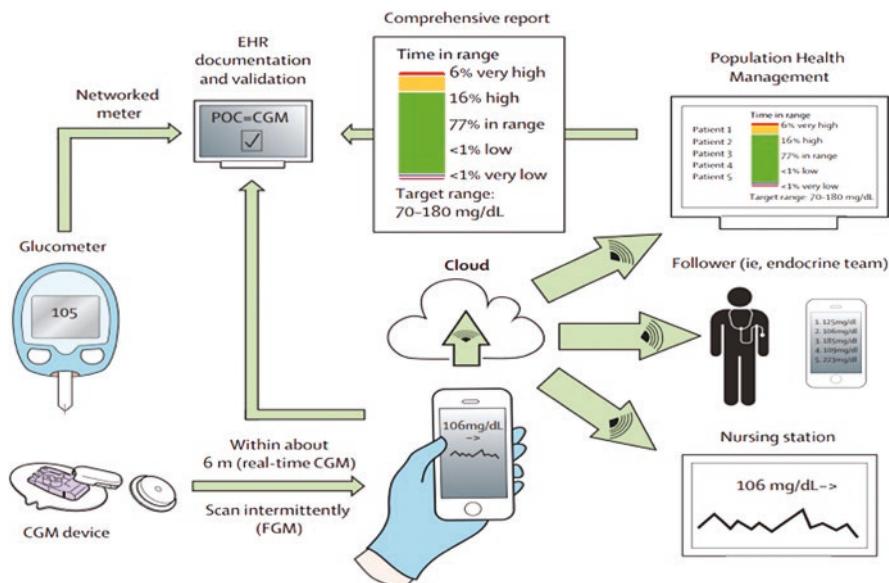


Fig. 8.1 Overview of remote glucose monitoring during the COVID-19 pandemic. Schematic for remote glucose monitoring in the hospital setting using a hybrid model with both CGM and POC glucose testing combined with remote monitoring of real-time and aggregate glucose data. [Reprinted with permission from Pasquel FJ, et al. Management of diabetes and hyperglycaemia in the hospital. Lancet Diabetes Endocrinol. 2021;9(3):174–88]

Additionally, several smaller studies have evaluated the use and accuracy of CGM during the perioperative period with results supporting ongoing CGM reliability postoperatively. Still there remains some concern regarding potential interferences during the operative period (e.g., electrocautery, induced hypothermia protocols) that may compromise sensor accuracy [14–16]. Together, these studies highlight the need for larger trials to identify clinical situations where alternative methods of glucose monitoring may be required.

Inpatient CGM investigation has expanded its clinical focus by addressing both hypoglycemia prevention and optimizing glucose trends, utilizing time in range (TIR) metrics, with the goal to increase the percent of time that the sensor glucose remains within the prespecified target of 70–180 mg/dL. More recent studies have utilized real-time CGM (RT-CGM) with remote monitoring capabilities to alert providers to glucose trends and hypo- and hyperglycemic glucose values, allowing for proactive management decisions (Table 8.2). A study by Singh and colleagues investigated the use of real-time CGM with a remote monitoring system, located at the nursing station, for the prevention of hypoglycemia in high-risk non-critically ill patients with T2D ($N = 72$) [17]. Results showed significant improvement in hypoglycemic events and glucose time below range (TBR) in the RT-CGM group compared to those receiving standard-of-care POC glucose testing, though no significant change in TIR (70–180 mg/dL) or time above range (TAR) was observed in this study. Three additional studies utilized CGM with remote monitoring and alerts for both hypo- and hyperglycemia to inform clinical adjustments by care teams. The study by Fortmann et al. showed improvement in mean glucose and TAR, but only significant improvement in TIR when defined between 70 and 250 mg/dL for those randomized to RT-CGM [18]. The study by Spanakis et al. again showed no significant change in TIR or TAR with the use of RT-CGM-guided insulin adjustments, though there was a reduction in TBR and recurrent hypoglycemia among patients experiencing one or more episodes of hypoglycemia during admission [19]. The study by Klarskov et al. included patients with diabetes and COVID-19, with no statistically significant difference in TIR, TAR, or TBR observed with RT-CGM [20]. Unlike the aforementioned studies, in this study, real-time CGM alarms were not utilized. In a pilot trial by Dillmann and colleagues in patients with T1D and T2D admitted for either acute complications or glycemic management education (including initiation of CSII), CGM data was transmitted to the nursing station permitting staff to respond to alerts for glycemic excursions based on a prespecified protocol outlined by the supervising physician [21]. Although there was no significant improvement in TIR for the whole group, subanalyses by diabetes and admission type demonstrated an improvement in TIR and TAR in those with T2D and in those admitted for acute complications. Together, these studies not only highlight the potential benefits of inpatient CGM with remote monitoring but also underscore the need for ongoing research regarding implementation and best processes for utilization of sensor glucose data.

Table 8.2 Non-critical care studies using RT-CGM to guide inpatient clinical management (past 5 years) and associated changes in glycemic control metrics

| | Population | Comparator | Results | ΔTIR (70–180 mg/dL) | ΔTBR (<70 mg/dL) | ΔTAR (>250 mg/dL) |
|----------------------|--|--|--|---|---|--|
| Singh et al. [17] | T2D at high risk for hypoglycemia ($N = 72$) | RT-CGM vs. POC | \downarrow Hypoglycemic events/patient (0.67 [95% CI 0.34–1.30] vs. 1.69 [1.11–2.58], $P = 0.024$) | \leftrightarrow | \downarrow | \leftrightarrow |
| Fortmann et al. [18] | T2D or hyperglycemia ($N = 110$) | RT-CGM vs. POC | \uparrow TIR (70–250 mg/dL; +11.26%) \downarrow Mean glucose (-18.5 mg/dL) \downarrow TBR (>250 mg/dL; -11.41%) | \leftrightarrow | \leftrightarrow | \downarrow |
| Dillmann et al. [21] | T1D ($N = 28$) and T2D ($N = 25$) admitted for acute complication (AC) or therapeutic education (TE) | RT-CGM at start vs. end of hospitalization | No significant differences in TIR, TAR, or TBR. Metrics varied by diabetes type and admission reason | $\Delta TIR: \downarrow$ $\Delta T2D: \uparrow$ $\Delta AC: \leftrightarrow$ $\Delta TE: \downarrow$ | $\Delta T2D: \downarrow$ $\Delta AC: \leftrightarrow$ $\Delta TE: \downarrow$ | $\Delta TID: \uparrow$ $\Delta T2D: \downarrow$ $\Delta AC: \downarrow$ $\Delta TE: \uparrow$ |
| Karskov et al. [20] | Diabetes (T1D, T2D, new-onset, gestational) and COVID-19+ ($N = 64$) | RT-CGM vs. POC | No significant differences in median TIR (46% [IQR; 15, 75] vs. 68% [14, 84.5], $P = 0.368$), TAR >180 mg/dL (52% [24, 85] vs. 31% [15.5, 86], $P = 0.386$) or TBR <70 mg/dL (0% in both groups) | \leftrightarrow | \leftrightarrow | \leftrightarrow |
| Spanakis et al. [19] | T1D and T2D ($N = 185$) on basal-bolus insulin | RT-CGM vs. POC | No significant differences in TIR (54.51% \pm 27.72 vs. 48.64% \pm 24.25; $P = 0.14$) or TBR <70 mg/dL (0.69% \pm 2.15 vs. 2.15% \pm 5.91; $P = 0.43$) | \leftrightarrow | \downarrow (those with ≥ 1 hypoglycemic event) | \leftrightarrow |

CGM in Critical Care Settings

In the critical or intensive care unit (ICU) setting, previous studies have investigated the use of not only subcutaneous CGM but also intravascular and transdermal CGM systems [10]. Similar to CGM data from the noncritical care settings, earlier studies focused on accuracy and glycemic control with very few reporting on clinical outcomes. CGM use expanded rapidly in the ICU setting during the COVID-19 pandemic, with studies indicating reasonable accuracy of subcutaneous CGM [22–26]. However, certain clinical conditions more commonly encountered during the management of critical illness (e.g., severe hypoperfusion, hypothermia, mechanical compression during positional changes) may interfere with sensor accuracy and function [5, 12]. A study by Faulds et al. evaluated a hybrid protocol for glucose monitoring combining RT-CGM with intermittent POC glucose testing in critically ill patients with COVID-19 requiring IV insulin infusion ($N = 19$) [27]. In this protocol, sensor glucose values were compared to POC at least once every 6 h to ensure good correlation (within 20% of reference value for glucose ≥ 100 mg/dL and within 20 mg/dL of reference value for glucose values < 100 mg/dL). Results indicated reliability of CGM with a significant reduction in the number of POC glucose tests required during IV insulin infusion (median of 7 POC glucose tests per day [IQR 6.16] vs. standard hourly POC testing). Following these findings, Davis et al. conducted a proof-of-concept study linking glucose values using the hybrid protocol to a computerized decision support system guiding IV insulin infusion in ICU patients with COVID-19 ($N = 9$) [5]. Additionally, this study implemented EHR documentation of CGM values and the validation protocol. Results showed good overall feasibility of CGM use with 75.7% of sensor glucose values > 100 mg/dL within 20% of the reference POC. The mean number of POC glucose tests per day was 8.24 ± 3.06 , reflecting a significant reduction in POC glucose testing typically required over a 24-h period during IV insulin therapy.

Data obtained from CGM use in the ICU during the COVID-19 pandemic has underscored the importance of confirming enduring CGM accuracy, particularly during times of clinical instability where unidentified factors may impact sensor reliability. This is particularly important given the continued interest in developing systems and protocols for CGM-guided insulin therapy to adapt to changing clinical situations, treatment plans, and insulin needs often encountered in the ICU. Larger clinical trials are needed to better understand CGM functionality among diverse inpatient populations, as well as how this technology can be effectively integrated into the critical care workflow.

Current and Future Considerations for Inpatient CGM

The transition of CGM devices designed for outpatient use into the hospital setting remains investigational at this time (Table 8.1). Many hospitalized patients desire continued use of personal CGM therapy during admission. Professional societies

and consensus guidelines have made recommendations for continuation of personal diabetes technology during hospitalization, overall favoring continuation of patient devices, including CGM if the patient can reliably manage their own technology [28–31]. It is also recommended that there be involvement of the hospital diabetes care or specialty teams to assist with management. However, frequently changing clinical scenarios, rapidly fluctuating glucose values, and significant glycemic excursions beyond CGM detection range necessitate ongoing POC glucose monitoring. Because CGM is not currently FDA approved for hospital use, there is no specific recommendation on how continued use of personal CGM devices may be utilized non-adjunctively, and there is a strong recommendation that hospital protocols for personal diabetes technology be in place for guidance [28–31].

As efforts continue to translate CGM to the hospital, there are important factors to consider during implementation (Fig. 8.2). The current approach for remote monitoring is effective but not necessarily practical for implementation. The use of a locked smartphone, the setup of online accounts, and additional devices not designed for louder alarms (tablet) could be improved for inpatient use [5, 32]. In addition, cybersecurity issues to avoid hacking of servers, electronic systems, networks, smartphones, and data need to be addressed and standardized. There are additional steps needed for the successful implementation of CGM with currently approved devices. Before initiating the process, the involvement of multiple stakeholders can facilitate identification of potential hospital-specific barriers and implementation needs. A previous study by Davis et al. reported on implementation of CGM use in the ICU settings for patients with COVID-19 [5]. In initiating this study, they identified relevant stakeholders for CGM approval (leadership: ICU staff, hospital administration, laboratory, safety officer), placement and use (nursing staff, pharmacists), EHR documentation (IT staff), training (nursing

| Remote Monitoring and Data Integration | Implementation and Education |
|--|--|
| Development of a hospital specific protocol for viewing and transmission of remote monitoring data | Multidisciplinary involvement/planning Hospital administration Medical teams Nursing leadership and staff Pharmacy Information technology Laboratory |
| Integration of CGM data into the EHR | Development of educational materials, protocols and training documentation |
| Standardization of inpatient CGM metrics and glucose targets | Ongoing evaluation of implementation strategies |
| Understanding best processes for utilization of CGM data to optimize glycemic control | |
| Accuracy/Reliability | Cost Analyses |
| Pathway to FDA approval | Identification of high-risk patients who may benefit most from CGM (hypoglycemia risk, high glycemic variability) |
| Identification of potential interferences | Analysis of CGM costs Device costs Implementation and personnel costs Hospitalization costs with and without CGM |
| Medications Procedures (imaging, surgical) Sensor compression Clinical factors (hypoperfusion, anemia, hypothermia) | RCTs for evaluation of hospital outcomes |
| Consideration of a hybrid CGM-POC protocol to ensure sustained sensor reliability | |

Fig. 8.2 Potential requisites for realization of inpatient CGM therapy

staff, endocrinology), ordering processes (industry partner, hospital administration), and remote monitoring (nursing staff, endocrinology). Multidisciplinary efforts were key in the design and initiation of this new clinical care process, and similar collaborations will be needed to move forward with technology implementation.

Documentation, EHR integration, and monitoring platforms are other necessary elements for use of CGM in the hospital environment. Having CGM data available to hospital care teams in real time via the EHR integration allows for efficient review of glucose data for clinical management. Traditionally, decisions on insulin adjustments for non-critically ill patients are based on POC glucose values every 6 h (patients not eating) or before meals and at bedtime. In the ICU, hourly glucose testing guides continuous insulin infusion adjustments every hour. With CGM, providers get access to 288–1440 values in 24 h, additional metrics (time in target ranges, glucose variability, mean glucose), trends, and alarms. The optimal use of this data for establishing target goals and strategies to achieve those goals is not known. There is a need to define alarm setup (low and high sensor glucose values) and the benefits or potential harm of real-time insulin adjustments (as opposed to daily adjustments) and to determine if there is any relevance on using other glycemic control metrics (including glycemic variability) for decision-making. Summary CGM data (over 24 h) has been used to guide daily insulin therapy adjustments [17–19]. This approach has confirmed to be non-inferior to decisions made based on POC testing [17–19]. In addition, the use of real-time data with alarms set at 85 mg/dL can prevent the risk of hypoglycemia in high-risk patients [17]. There is a need to define the appropriate hospital time in range for most patients and potential adjustments to these targets according to underlying clinical characteristics and hypoglycemia risk.

Integration of CGM with insulin pump therapy for automated insulin delivery (AID) is changing the management of T1D and is now expanding to T2D in the outpatient setting [33–36]. Patients admitted to the hospital with personal AID systems may be able to continue wearing them during hospitalization, but there is a need to standardize the processes for safe use and documentation of CGM glucose values and insulin delivery in the hospital. Consensus guidelines have outlined recommendations not only on the use of personal CGM in the hospital but also on insulin pumps (including AID), which are discussed in Chap. 7. There is continued interest in translating and adapting this technology for hospital use as well, with previous European trials showing improvement in glycemic control in hospitalized patients. However, safe functionality of AID relies on accurate sensor data for algorithm-directed insulin infusion. It may be reasonable to consider a hybrid protocol similar to the one implemented in ICU studies during COVID-19 to assess ongoing CGM reliability for adjustment of insulin infusion in the hospital.

Conclusion

Investigation of CGM use in the hospital has accelerated in the last few years, partly related to the significant advancements in device accuracy and integration with digital health for remote monitoring, as well as rapid implementation of CGM during the COVID-19 pandemic to reduce PPE waste and risk of healthcare provider infection when vaccines were not yet available. With the recent information on accuracy of several devices in the hospital, as well as initial trials showing benefits in hypoglycemia risk reduction, the landscape for the use of this technology is expanding rapidly. Although there are some concerns about potential known and unknown interferences with CGM devices in the hospital, the path to FDA approval appears feasible considering the wealth of knowledge gained suggesting that the technology is safe, effective, and reliable. For now, adjunctive CGM therapy with periodic capillary glucose confirmation is recommended (i.e., hybrid protocols) while we continue to learn how to best translate this technology into the hospital to ultimately improve the care of hospitalized patients with diabetes and reduce the burden of care for hospital staff. Disclosures GMD is supported by the National Institutes of Health (NIH) under Award Number K23DK122199 and has received research support from Insulet Corp. and consulting fees from Medscape, Inc.

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Chapter 9

Computer-Guided Approaches to Inpatient Insulin Management



Jagdeesh Ullal and Joseph A. Aloi

Introduction

Over the past decade, insulin dosing calculators have been developed and increasingly deployed in hospitals and hospital systems across the country. Their rapid adoption has been driven by patient safety, ease of integration into electronic health records (EHRs), ability to track metrics, faster patient throughput, and lower diabetes healthcare costs. In large part, the Health Information Technology for Economic and Clinical Health Act passed in 2009 was responsible for adopting, implementing, and promoting meaningful use of electronic health records across the United States [1].

Three aspects of EHRs, computer decision support (CDS) tools, computerized physician order entry (CPOE) systems, and health information exchange, are mediators of change in the healthcare system. CPOE represented a dramatic change in the workflow of providers from paper-based order entry systems to computerized order entry. CPOE paired with CDS forms the fundamental basis of all modern electronic glucose management systems (EGMSs).

In this chapter, we discuss the various commercially available and internally developed EGMSs that are used for both subcutaneous and intravenous glucose management in the United States. We discuss the pitfalls and benefits of EGMSs, as

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well as the potential cost savings, patient safety aspects, and rationale for the adoption of EGMS.

Subcutaneous Insulin Dosing Calculators

In the 2022 Endocrine Society Clinical Practice Guidelines for Inpatient Hyperglycemia, the working group recommended a goal of inpatient blood glucose of 100–180 mg/dL in patients admitted to noncritical care settings [2]. For patients with hyperglycemia and no prior history of diabetes mellitus (DM), the initial treatment recommendation is correction insulin with the gradual escalation of treatment. For patients with diet-controlled or non-insulin-treated DM, the recommended treatment is correction insulin or scheduled insulin dosing; insulin-treated DM is managed inpatient with basal-bolus insulin (BBI). The CDC reports that 37.3 million people in the United States have DM, with increased trends in hospital admissions [3].

Inpatient insulin therapy can be challenging due to the dynamic status of persons with hyperglycemia including variations in nutrition [oral, enteral, parenteral, or periods of nil per os (NPO)], changes in renal function, introduction of medications such as glucocorticoids that affect glucose control, multiple consultant groups involved in the care, and inpatient procedures that also influence the dynamics of glucose control. All these factors potentially lead to insulin-related dosing errors leading to either hypoglycemia or hyperglycemia. These events increase morbidity and mortality, add to the cost of healthcare, strain hospitals, and stress clinicians taking care of patients.

Technological advances defining insulin dosing by software or calculators have been developed to overcome some drawbacks described above with varying degrees of built-in patient safety features [4]. These include auto-population of glucose values from the EHR, assessing the current dose and recommending the next dose of insulin, recommendations for treatment of hypoglycemia, alerts to prevent inadvertent low sugars or high sugars, and alerts to avoid missed insulin doses or blood sugar testing.

FDA-cleared inpatient subcutaneous insulin EGMS tools include Glucommander™ (Glytec), GlucoStabilizer (Medical Decision Network), EndoTool® (Monarch Medical Technologies), GlucoCare™ (Pronia Medical Systems), and Core Diabetes App (Transformative Med). The Core Diabetes Application complies with FDA CDS rules but has not sought FDA approval or clearance because it does not provide automatic insulin dose adjustments.

Features of these software packages include the presence of dashboards that graph glucose trends, doses, and other helpful information that provide a single-screen snapshot. Alerts flash on the same screen referred to as a dashboard, minimizing the need for additional “pop-up” signs that might lead to alerting fatigue.

The Glucommander subcutaneous dosing software has been shown to be comparable, if not better, than provider-managed basal-bolus insulin dosing with lower

hypoglycemia incidence and improved blood sugar control [5]. Implementation of the subcutaneous Glucommander tool results in less sliding-scale insulin (SSI) and better transition to basal-bolus insulin treatment [6]. The Glucommander tool adjusts basal insulin doses daily; mealtime insulin and correction doses change based on the number of carbohydrates entered for the given meal and the current glucose level. Weight-based dose recommendations are provided for an initial dosing strategy, but the program can also titrate doses if the provider enters basal and mealtime insulin doses. There are warnings and alerts for missed doses and hypoglycemia. Subcutaneous Glucommander should not be used to treat hyperglycemia related to enteral or parenteral nutrition. SmartClick is a functionality in Glucommander that allows single sign-on and access to eGMS within the EHR. Lab results such as hemoglobin A1c, blood glucose, and anion gap are imported into Glucommander from the EHR. Integration with the medication administration record (MAR) sends dose confirmation to Glucommander. Glucose values are auto-populated into Glucommander but require bedside nurse confirmation as a safety check. If glucose values were performed more than 15 min prior to insulin administration, a recommendation is made to recheck glucose within 15 min of treatment. Glucommander is indicated for both pediatric and adult age groups.

EndoTool SubQ software has also been shown to reduce hyperglycemic and hypoglycemic episodes while increasing time in target and reducing length of stay [7]. EndoTool is approved for both pediatric and adult patients. It can factor in diet, enteral vs. parenteral nutrition, and intravenous dextrose, an advantage over other software. The initial dose recommendation is based on clinical variables, including the type of diabetes, kidney function, nutrition plan, and presence of steroids.

GlucoStabilizer uses a subcutaneous insulin dosing software known as Clarian GlucoStabilizer Subcutaneous Insulin Program, which allows dose calculations and alarms with built-in default for insulin sensitivity factor and insulin-to-carb ratio but limited ability to change basal insulin doses [8, 9]. GlucoStabilizer has an algorithm for adults and a separate algorithm for children above the age of 2.

Some EHRs have locally developed insulin dose calculators built-in or embedded into EHR. These insulin dose calculators integrate with order sets. Using EHR-integrated dosing calculators has been shown to increase patient and provider satisfaction [10]. Furthermore, integration into EHRs allows an accurate record of insulin doses recommended versus administered and double verification of glucose before insulin is given.

Intravenous Insulin Dosing Calculators

In the early 2000s, the Leuven trial established the benefit of intensive intravenous (IV) insulin therapy in the critical care setting, creating a need for intravenous insulin protocols that achieved goal-based glucose control [11]. However, the follow-up NICE-SUGAR trial established that tight glycemic control in the intensive care unit (ICU) was not beneficial, and the risks of hypoglycemia with lower glucose targets

lead to increased morbidity and mortality [12]. Conversely, data on the patient population treated with intravenous insulin specifically in the setting of open-heart surgery showed that tight glucose control is beneficial in preventing wound infections [13, 14]. The fundamental basis of intravenous insulin dosing is the use of the Davidson equation, which calculates insulin rate (IR) as follows: $IR = [BG-60] \times ISF$. The ISF is often referred to as a “multiplier” in the Glucommander algorithm. Here, we discuss Glucommander, EndoTool, GlucoStabilizer, and GlucoCare, which are FDA-cleared commercially available IV insulin dosing EGMS.

Glucommander IV tool, compared to paper-based IV insulin infusion algorithms, is superior to achieving euglycemia faster and with lower rates of hypoglycemia in diabetic ketoacidosis (DKA) [15]. IV Glucommander can be used for patients on continuous enteral or parenteral nutrition or bolus enteral feeds. However, it is recommended that for nocturnal or cycled/intermittent enteral or parenteral nutrition, standard insulin management is recommended outside Glucommander. Furthermore, steroid-induced hyperglycemia should be treated with insulin outside Glucommander particularly if steroid doses are being changed. Transition off IV to the subcutaneous module is guided by the software based on certain parameters including controlled sugars for a continuous 2–4 h, reasonably stable drip rate, closed anion gap with no acidosis, and no meal bolus being administered. Some institutions avoid transitioning overnight and instead prefer to transition at around 7–8 a.m. when the early-morning drip rate is stable and there is no meal bolus that is active. Transition can be done with any long-acting insulin. For example, if glargine insulin is administered, the drip continues for 2 h until the onset of glargine insulin and recommendations are made to transition to the subcutaneous module. NPH insulin can also be chosen as a basal insulin, and the choice of twice-daily or once-daily basal insulin is available. Many of these safeguards promote a smooth transition, thus avoiding loss of glycemic control.

GlucoStabilizer operates through a secure server rather than a cloud-based program. The IV insulin doses are calculated by the software considering the varying changes in the patient’s status, nurse input, and glucose trends. The outcomes of GlucoStabilizer use include improved time to target glucose, lower frequency of hypoglycemia, and improved length of stay. There is an easy module of transition from the IV to subcutaneous dosing module called CGS-SQ [16].

EndoTool IV insulin management software has separate algorithms for the pediatric age group and adults. This software algorithm factors in blood glucose, type of diabetes, dose of insulin, hemoglobin A1c, height and weight, kidney function, age, and diet to calculate insulin dosing.

GlucoCare is an FDA-cleared insulin dosing calculator based on the Yale Insulin Infusion protocol [17]. Initially designed to target a goal of 100–140 mg/dL, it was later refined to achieve a slightly higher goal of 120–140 mg/dL and a specific glucose level of 140 mg/dL rather than a range. A unique feature of GlucoCare is the addition of a mid-protocol bolus insulin during treatment to reduce high insulin rates in insulin-resistant patients, while most other software recommend a starting bolus [18]. GlucoCare is installed on hospital servers but is cloud based. The rates

of hypoglycemia are low, and the mean glucose level achieved is around 140–150 mg/dL with GlucoCare.

At institutions such as the University of California San Diego Health and the University of Michigan, insulin infusion computer calculators are built-in directly or embedded in the EHR, which yield comparable outcomes to conventional paper-based algorithms [19, 20]. This results in higher staff satisfaction, better protocol compliance, increased glucose time in range, and reduced hypoglycemia. Some institutions have used separate software that is not integrated into the EHR. One example is the GENIE protocol at the Veterans Affairs Hospital, Pittsburgh VA, which has been shown to be superior to conventional IV insulin protocols with improved glycemic control and outcomes with open-heart surgery [21]. Locally designed and built IV insulin protocols may result in closer and more coherent integration with EHRs, better nursing satisfaction, and improved patient safety [22–25]. At the University of Pittsburgh Medical Center, we have developed a simple Web-based tool that mirrors paper-based IV insulin protocols. When initially implemented, there was good acceptance by ICU nurses and providers [26].

Disease-Specific Studies and Outcomes with IV Calculators

Glucommander has been studied in DKA in the emergency department setting as well as in the ICU. One small study showed that patients treated with mild DKA in the ED could be discharged after an average period of 5 h and 11 min on the Glucommander IV insulin protocol with a low incidence of hypoglycemia and a cost-saving benefit [27]. Another multicenter retrospective trial with hospitalized patients treated with Glucommander showed lower hypoglycemia and faster rates of DKA resolution compared to the paper-based algorithm [28]. Similarly, in mixed medical ICU, patients with Glucommander treatment yielded tighter glycemic control without significant risk of hypoglycemia [29]. Glucommander has been extensively studied in patients post-cardiovascular surgery. Several studies show the efficacy of using Glucommander in the cardiothoracic ICU (CTICU) [30, 31]. The GLUCO-CABG trial in the CTICU was an open-label randomized trial between intensive insulin therapy-treated CABG patients comparing a target glucose of 100–140 mg/dL versus 141–180 mg/dL [32]. The results did not show a significant reduction in perioperative complications, but subgroup analysis did show lower complications in people without diabetes.

Glucommander has also been tested in allogeneic hematopoietic cell transplantation, where there is a need for supraphysiologic doses of steroids for immunosuppression [33]. In this study, Glucommander was used to examine the number of patients who would achieve tight glucose control of 100–140 mg/dL in the context of complicated clinical circumstances of high-dose steroids, unpredictable oral nutritional intake, and parenteral nutrition while avoiding hypoglycemia. The authors concluded that the Glucommander algorithm achieved the preset glucose range 61% of the time, ten episodes of hypoglycemia under 70 mg/dL, and no

glucose levels under 40 mg/dL. Similarly, GlucoStabilizer has been successfully tried in treating DKA, yielding comparable results to other EGMSs [34]. In addition to DKA, GlucoStabilizer has also been studied in treating gestational diabetes mellitus in pregnant women using intrapartum IV insulin treatment [35]. This group of patients need tighter glucose targets due to the stringent glucose goals in pregnancy. In this small cohort, a significant proportion of patients treated with the GlucoStabilizer algorithm reached target glucose compared to standard IV insulin treatment without significant maternal or neonatal hypoglycemia or other neonatal complications. The “SHINE” trial examined the efficacy of GlucoStabilizer compared to sliding-scale insulin in patients with stroke [36]. The study did not show any benefit of tight glucose control on stroke outcomes, but the incidence of severe hypoglycemia was higher with intensive insulin treatment [37]. EndoTool has also been shown to be efficacious in the management of DKA and hyperglycemic hyperosmolar syndrome (HHS) compared to paper-based protocols [38]. Table 9.1 summarizes features of both IV and subcutaneous versions of various EGMSs.

Advantages and Disadvantages of Insulin Dosing Calculators

Apart from the benefits of glucose control and low incidence of hypoglycemia, one potential benefit of using insulin dosing calculators and EGMSs that are integrated into the EHR is the minimization of human error in dose calculations and improved nursing adherence to the protocol [5, 39]. Double confirmation of auto-populated glucose levels adds an extra level of safety. Some hospitals may require double verification of IV insulin dose changes.

Many EGMSs have built-in alerts for nurses to check blood glucose and reminders for timely insulin dosing [39]. On-screen prompts to enter carbohydrates and meals eaten prevent inadvertent mealtime insulin dosing for missed meals. If patients are eating meals, specific IV insulin software allows for meal boluses during the IV insulin run, preventing the drip rates from going up inadvertently but rather in a calculated approach such as a square-wave bolus.

In treating DKA, many protocols have message alerts to correct hypokalemia before IV insulin is initiated. If the insulin doses are widely variable or fluctuating, or if the anion gap is not closed or acidosis is not resolved, alerts are presented to providers who are discontinuing IV insulin or transitioning to subcutaneous insulin. Such safeguards prevent DKA recurrence or rebound hyperglycemia with IV insulin discontinuation.

Many EGMSs that have both IV and subcutaneous dosing calculators have a tool that helps transition from IV insulin to basal-bolus insulin. Transition to BBI is an important step that clinicians should make carefully [40]. Many EGMSs will recommend a transition dose based on the current clinical characteristics, IV insulin drip rate, and blood sugar trends [41]. Providers may accept or edit the recommended doses. Options for once-daily or twice-daily basal dosing are available

Table 9.1 The various features of commercially available EGMSs

| eGMS software | Company | Interoperability/integration | Analytics/extensions/features | IV/subcutaneous | Age group | Treatment of hypoglycemia |
|-----------------|---|--|---|---------------------|---|---|
| Glucomander | Glytec, Greenville, SC | Cloud-based, EHR integration, HL7 laboratory data, HL7 ADT | GlucoMetrics (analytics), GlucoSurveillance (at-risk patient identification), GlucoView (workflow alerts) SmartClick (SSO access from EHR) | IV/ subcutaneous | Adult and pediatrics | Hypoglycemia protocol in both IV and subcutaneous version. Correction formula: $50\% \text{ BG level} = (100 - \text{BG}) \times 0.2 \text{ g}$; treatment recommendation provided |
| EndoTool system | Monarch Medical Technologies, Charlotte, NC | Citrix server | EndoTool analytics, estimated residual extracellular insulin (EREI) to estimate active insulin, modules to treat DKA/HHS | IV/ subcutaneous | Adult and pediatrics (>2 years or >12 kg) | Built-in safeguards for hypoglycemia prevention |
| GlucoStabilizer | Medical Decision Network, Charlottesville, VA | Secure server | | IV only | Adult and pediatrics | Built-in safeguards for hypoglycemia prevention |
| GlucoTab | Decide Clinical Software GmbH, Graz, Austria | Mobile tablet/Web interface; HL7 laboratory data, HL7 ADT | Basal-bolus, basal only, electronic drug prescription recommendations, bolus calculator | Subcutaneous only | Adult and geriatric (basal only) | Built-in safeguards per protocol which results in lower hypoglycemia |
| GlucoCare | Pronia Medical Systems, Inc., Lewisburg, PA | HIPAA-compliant cloud-based platform or standard server model or locally maintained cloud-based platform | Embedded quality improvement/assurance features | IV only | Adults | Built-in protocol for hypoglycemia prevention |

along with mealtime insulin dosing. Some EGMSs have algorithms for enteral feeds and steroid-related hyperglycemia.

Studies have shown an improved length of stay or shorter hospitalization, lower cost to patients and insurers, and fewer emergency department visits or rehospitalizations. Some EGMSs have tools to help with discharge recommendations for diabetes based on current dosing trends [42]. Many EGMSs have an additional feature for institutions, hospitals, and health systems to analyze and report “glucometrics” or glucose-related performance metrics. These are key performance indicators that institutions may have to report to Centers for Medicare & Medicaid Services (CMS) or maintain and keep track of the current and desired state of glycemic performance.

Despite all the benefits of implementing an EGMS, we do not see widespread use of these dosing calculators. Many disadvantages of switching from conventional insulin dosing using electronic order sets or paper-based treatment algorithms to an EGMS are as follows:

- Cost: The cost of EGMS implementation is usually priced by the number of beds in the hospital per year or in some cases the number of units that are adopting the system. Usually, the cost runs into hundreds of thousands of dollars depending on the size of the hospital or hospital system on an annual basis.
- Therapeutic and institutional inertia: a major obstacle to the day-to-day success of running an EGMS is dependent on the staff. Healthcare providers often have inertia to adopting change. Some of this inertia is due to a lack of readiness to adopt a new process or to relinquish control and the habit of being comfortable with status quo [43]. Before an EGMS is implemented, a plan to “retire” or “sunset” previous order sets and protocols should be made to allow staff to be prepared to smoothly transition to EGMS. A hybrid option which allows for use of paper protocols and EGMS can lead to confusion and a lack of adoption of EGMS.
- The time and expense related to education and reeducation of staff: EGMS can be nursing intensive, and bedside nurses need more education and training than providers before and after implementation. Incorporation of EGMS education into nursing orientation after hire is very helpful. Problem-solving skills should be discussed. This will reduce post-implementation helpline calls. Provider education on the other hand is not as intense as nursing education. Providers benefit from learning about the science, efficacy of EGMS, and ordering process in EHRs.
- The IT-related cost: Most EGMSs offer a comprehensive option to integrate with EHRs. However, if a third-party software such as Tidepool or Glooko is used, then additional cost may be incurred. There may also be IT fees to add servers for different levels of integration into the EHR or for communication with laboratory interfaces. Hardware upgrades, need for dedicated computer terminals, tablets, or laptops may involve additional cost.

For homegrown EGMS, there is a need for frequent upgrades and integration as connectivity changes or newer devices replace older ones. Extensive IT support is

required to integrate EGMS into existing EHRs. Laboratory and test-resulting software and pharmacy software are often separate and need integration to auto-populate glucose values and doses. All these steps require constant maintenance, collaboration, and oversight from a multidisciplinary task force or patient safety committee [44, 45]. Buy-in from nurses is a key factor of success [6]. Frequent alerts can result in nursing alert fatigue. EGMS may not be able to accommodate sudden changes in the clinical status of patients or additions of new medications that raise or lower blood sugars. All EGMSs rely on manual data entry; thus, using EGMS cannot eliminate human error. Errors at the end-user level, such as the nurse or pharmacist, can still lead to wrong doses or wrong type of insulin being administered to the wrong patient despite correct EGMS recommendations.

Conclusion

Electronic glucose management systems can be valuable tools to help clinicians manage inpatient diabetes and hyperglycemia. There are commercially available software that could be integrated into EHRs or used as standalone software. Many institutions have developed IV insulin, subcutaneous insulin dosing, and calculators. Both commercial and homegrown calculators require a considerable investment of money, time, and effort, but if used efficiently can lead to the benefits of lowering costs related to diabetes and overall improvement in diabetes care. A nationwide shortage of inpatient endocrinologists is a challenging problem for many hospitals and hospital systems [46]. The COVID-19 pandemic has taught us the utility of telemedicine in the care of hospitalized people with diabetes, but a compelling inpatient glucose management strategy can be challenging to achieve without a significant investment of time by glucose management teams [47–50]. Glucose management software can bridge this divide if institutions overcome the initial hurdles by deciding a strategy that is right for them. We are moving to an age of artificial intelligence in diabetes care [51]. This new wave may bring us a future that we must prepare to accept and use conventional wisdom to steer toward safe quality-centric care for our patients.

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Chapter 10

Remote Glucose Management for Hospitalized Patients



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Introduction

Diabetes affects about 10% of the general population in the United States, and more than 30% of non-critically ill hospitalized adult patients experience hyperglycemia [1, 2]. Traditional strategies for inpatient glucose management such as inpatient diabetes specialists, diabetes teams, and endocrinology in-person consultations are time and resource intensive and fail to meet the increasing demand of hospitalized patients requiring glucose management. As such, innovative remote approaches have been introduced to establish safe, scalable, and efficient glucose management systems. The development of reliable remote glucose management systems gained even more attention during the coronavirus disease 2019 (COVID-19) pandemic as it reduced unnecessary exposure to possible infection for both patients and providers. In this chapter, we review the different types of remote glucose management and future directions.

Beyond the traditional formal inpatient in-person consultation by either an inpatient endocrinology consultation service or a glucose management service, synchronous and asynchronous remote consultations are now being performed (Fig. 10.1).

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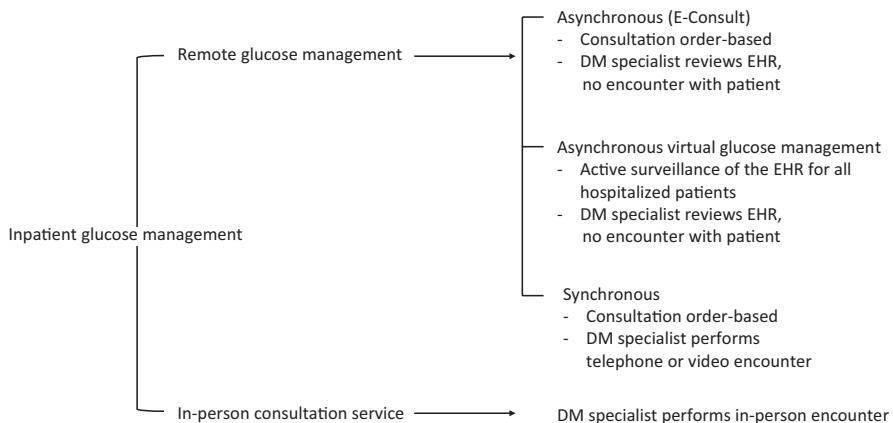


Fig. 10.1 Methods of inpatient glucose management and/or consultation

With a remote synchronous consultation, the in-person patient encounter is replaced by a video or telephone encounter. On the other hand, the most recently developed method, asynchronous virtual glucose management of hospitalized patients, refers to glucose management in which the diabetes provider does not have any encounter with the patient. Instead, a list of patients with suboptimal glycemic control is automatically generated from the electronic health record (EHR) based on predetermined criteria, such as hypoglycemia in the last 24 h. The diabetes provider works remotely, performing a focused review of pertinent data in the EHR for patients captured on this list. If required, the diabetes provider places recommendation notes in the EHR. Beyond that recommendation note, usually no direct contact with the patient or primary providers of the patient is made.

Remote Asynchronous Glucose Management

The earliest model of remote asynchronous glucose management may be in the form of e-consultation. E-consultation is when a diabetes specialist is consulted to provide recommendations based on the review of the patient's EHR without any encounter with the patient. The recommendations are shared to the primary team in a recommendation note (e-consultation note). Prior to the COVID-19 pandemic, e-consultations were relatively more widely used in the outpatient setting and had gradually started adaptation to the inpatient setting [3, 4]. The COVID-19 pandemic catalyzed the expansion of inpatient e-consultations including those for glucose management [5].

The more recently developed form of remote asynchronous glucose management, the (asynchronous) virtual glucose management, has consistently shown to improve glycemic control when implemented in addition to the traditional

consultation-based systems. It is being increasingly used (in various forms) by medical centers [6–8]. The key difference between e-consultation and virtual glucose management is whether a consultation order is required. E-consultation is initiated by the primary care team placing a consultation order. However, virtual glucose management is based on active surveillance of glucose data of all hospitalized patients. The active surveillance and identification of patients with inadequate glycemic control allow diabetes providers to review patients' glucose management without receiving a consultation order.

Based on a Daily Inpatient Glycemic Survey (DINGS), Mendez et al. compiled a daily report of patients with poor glycemic control (glucose <70 mg/dL or glucose >350 mg/dL in the past 24 h) [6]. Diabetes providers performed a focused review of each patient's electronic chart including glucose trends, medications, diet, and comorbidities. The diabetes providers then wrote a recommendation note when applicable, but did not change the orders themselves. The recommendation note was visible to any provider accessing the patient's electronic chart, and the expectation was for the primary care team to read the note and implement changes as appropriate. Depending on the clinical urgency of the glucose trend, the diabetes provider contacted the primary care team directly when necessary. After implementation, the risk of severe hyperglycemia (glucose >350 mg/dL) decreased by 30% and the risk of hypoglycemia (glucose <70 mg/dL) decreased by 47%.

Rushakoff et al. reported significant improvements on glycemic control after implementing a virtual glucose management service (vGMS) [7]. Utilizing a daily report that listed all patients who in the past 36 h had two or more glucoses ≥ 225 mg/dL or a glucose <70 mg/dL, each patient's EHR glucose flowsheet was reviewed by the vGMS team in detail. The vGMS team consisted of three providers, an endocrinology physician, a nurse educator, and a pharmacist diabetes educator. The glucose flowsheet contained all information required for glucose management such as details on insulin (i.e., separate rows showing nutritional, correction, and total rapid-acting insulin) or any glucose-altering medication (with dose and administration time), enteral feeding (rates of administration), meal consumption (percent of meal consumed), and recorded glucose levels. After implementing the vGMS, the proportion of patients with hyperglycemia decreased by 39% and the proportion of patients with hypoglycemia decreased by 36%. The time for this activity was between 30 and 45 min per day, and unlike the previous example above, there was no direct contact with the patient's provider nor any increase in formal consultations.

Following the work of Rushakoff and colleagues, Sheu et al. reported similar results after implementing a modified vGMS [8]. The modified vGMS was based on an electronic glucose dashboard that can be used to identify patients with poor glycemic control (two or more glucoses ≥ 300 mg/dL or a glucose <70 mg/dL during the previous 24 h). The study reported 25% reduction in the proportion of patients with hyperglycemia and a 45% reduction for hypoglycemia. The electronic glucose dashboard also generated chart visualization of the proportion of patients achieving glycemic management goals in different care units.

There are some common shared features amongst different virtual glucose management tools that contribute to the successful application of virtual glucose management. In the latter two models discussed above, diabetes providers performed chart review in the early morning and set a specific aim to complete recommendation notes before the time of morning rounds by the primary care team. This early-morning workflow is intended to maximize the visibility of the recommendation notes during morning rounds. In addition, the virtual consultant's documentation from all three studies specified that the recommendations are based only on electronic chart review and should be considered in the context of the primary care clinician's bedside assessment.

It is also important that the virtual glucose management is implemented without a significant increase in provider workload, both for the primary care provider and the diabetes specialist. A robust glucose flowsheet plays a key role in establishing a seamless workflow for the diabetes specialist when they review each patient's chart. With a well-curated visualization of relevant data in one display, the diabetes provider does not have to visit multiple parts of the EHR to gather information. In one study of virtual glucose management where a glucose management flowsheet was not available [6], the study reported approximately 15 min to review each patient's chart and to submit a recommendation note. On the other hand, another study reported a total daily time of 30–45 min to review the charts of all patients with poorly controlled glucose and to place recommendation notes as needed [7]. It is impossible to compare these two studies head-to-head as they were carried out at different institutions with radically different EHR systems (one was at a Veterans Affairs medical center and the other was at an academic medical center with commercial EHR use, allowing for much more customization such as the glucose flowsheet). Nonetheless, it brings attention to the importance of a strong EHR infrastructure to maximize the efficiency of virtual glucose management. In addition to building the glucose flowsheet, establishing standard insulin order sets and optimizing the documentation of medication administration collectively support the success of a virtual glucose management tool.

Although there are data to support improved glycemic control with the successful implementation of virtual glucose management, well-conducted studies investigating the benefits of virtual glucose management on hospital length of stay, in-hospital morbidity, or financial implications are lacking. However, as shown above, these virtual glucose management systems are scalable and could lead to significant cost savings as payments to hospitals become bundled where a single payment is made for all aspects of inpatient care (including physician payment). In addition, in integrated systems and national health systems where fee for service is not a consideration, traditional in-person consultations are costs to the system and virtual consultations may be cost saving. New CPT (Current Procedural Terminology) codes have been developed that now allow billing for reimbursement for asynchronous consultations where there is no contact with the patient and a written report but no other contact with the medical teams.

Remote Synchronous Glucose Management

Though not truly virtual, another model of remote inpatient glucose management is when there is synchronous engagement with the patients. In this case, the diabetes specialist has an encounter with the patient either with audio or with both audio and video elements. Most providers are familiar with this format of consultation as the only difference in this approach compared to the traditional in-person inpatient consultation is the mode of communication between the patient and the diabetes specialist. This approach is similar to e-consultation in that a consultation order from the primary care team is required. A group of large medical centers in Australia successfully transitioned to remote inpatient diabetes management, including telephone or video communication with patients when necessary [9]. In one center in the United States, with the start of the COVID-19 outbreak, inpatient glucose management was transitioned to a combination of both remote and virtual management. There was no difference in glycemic outcomes compared to their prior system of a formal inpatient diabetes service [10].

Automation

With all the available data, the natural question is if these systems can be automated. In one medical center, a clinical decision support system (CDS) was developed to recognize the glucose trend of each patient and display automated recommendations for hyperglycemia or hypoglycemia. It also screened electronic orders, which enabled identification of patients with inappropriate insulin orders, such as patients with type 1 diabetes who are only receiving correctional insulin [6]. When the criteria are met, the CDS displays an alert message for the primary care provider, but it does not automatically place orders or override any existing orders. Implementation of this CDS resulted in decrease of recurrent hyperglycemia (glucose ≥ 180 mg/dL at least twice, 3 h apart) by 10% in patients with diabetes. In addition, hypoglycemia (glucose ≤ 70 mg/dL) decreased by 43% in patients without the diagnosis of diabetes.

Conclusion

The increasing volume of hospitalized patients requiring glucose management has invoked the development of novel approaches for remote glucose management in the inpatient setting. Concurrent increase in the use of EHR has enabled active surveillance and identification of patients with out-of-range glucose trends. In addition to active surveillance, glucose control-related data in the EHR can be conveniently displayed on a glucose care flowsheet. The traditional model of consult-based

endocrinologist involvement in glucose management has also expanded its applicability by incorporating telemedicine technologies. Despite the recent innovations, inpatient glucose management remains a complex process given the frequent changes in clinical status, diet, and medications in hospitalized patients. While some newly developed CDS tools appear to be useful, due to this complexity, the current remote glucose management models still require varying degrees of diabetes provider involvement.

Finally, it should be recognized that these virtual glucose management services are generally not actively involved in ongoing management of the patient. These services deliver education to the inpatient providers just as they need it to help them with glucose management. Surveys of providers show that the vGMS leads to fundamental improvements in how the providers manage their patients, thus leading to fewer patients in need of these virtual glucose management services or traditional consultations [11].

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Part III

Inpatient Diabetes Management

in Unique Populations

Chapter 11

Diabetes Management in the Emergency Department



Dana Gottlieb, Robert Silverman, and Rifka C. Schulman-Rosenbaum

Emergency Department Approach to Diabetes Mellitus-Related Emergencies

Introduction

As the incidence of diabetes mellitus (DM) has risen over the past several decades, so has the number of emergency department (ED) visits for DM-related emergencies, including diabetic ketoacidosis (DKA), hyperosmolar hyperglycemic state (HHS), and hypoglycemia. It is essential for the ED provider to promptly identify and treat these conditions, as well as any underlying etiologies, as failure to do so increases morbidity and mortality [1, 2].

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Hypoglycemia

Hypoglycemia is a clinical syndrome of altered autonomic function and impaired cognition that occurs as serum glucose falls below normal physiologic thresholds. Hospital admission for severe hypoglycemia is a greater risk for mortality than hospitalization for hyperglycemia among Medicare patients in the USA [3]. Hypoglycemia is frequently managed in the acute care setting, and while rates of hospital admission for hyperglycemia have decreased by 39% between 1999 and 2011, admissions for hypoglycemia have increased by 12% [3]. Symptoms of hypoglycemia may occur at varying serum glucose levels in people with or without a history of DM and should be considered in any patient with altered mental status (AMS). It most commonly occurs in patients with known DM, primarily in those who use insulin or insulin secretagogues (i.e., sulfonylurea) for their DM treatment, and is a potentially life-threatening condition which can lead to coma and death [2–6]. While hypoglycemia may occur in patients without DM (Table 11.1) and is defined differently in that population, this chapter focuses on the ED management of hypoglycemia in patients with DM, defined as blood glucose (BG) <70 mg/dL [4, 6].

The initial approach to hypoglycemia in the ED includes obtaining vital signs, a history, and performing a physical exam. In the case of AMS or unresponsiveness, the primary survey should evaluate the patient's airway, breathing, and hemodynamics. This should be completed in conjunction with a point-of-care (POC) glucose test and an EKG [7].

As part of the history, it is prudent to investigate the patient's dietary habits, current medications (including dosages and adherence), recent infections, infectious symptoms, and past medical history. Screening for known symptoms of hypoglycemia, including neuroglycopenic symptoms such as AMS, lethargy, confusion, headache, dizziness, focal neurologic deficits, visual disturbances, seizures or unresponsiveness, and autonomic/cholinergic manifestations, including abnormal heart rate (tachycardia or bradycardia), anxiety, palpitations, diaphoresis, tremors, nausea, or vomiting, is warranted [4, 7, 9, 10].

Once hypoglycemia is identified, the critical short-term treatment goal is to increase the patient's glucose level. The method in which this is done depends on multiple factors, including mental status, ability to tolerate oral methods of glucose administration, and medical determination of need for nothing-by-mouth (NPO) status. In an awake and alert patient who can tolerate oral methods (PO),

Table 11.1 Possible precipitants of hypoglycemia [4, 5, 7, 8]

| | |
|---------------------|--|
| Adverse drug effect | Insulin, oral secretagogue, beta-blockers, ACE inhibitors, alcohol |
| Illness | Sepsis, myocardial infarction, renal failure, hepatic failure, adrenal insufficiency |
| Malignancy | Insulinoma, IGF-2 producing tumors, large tumor burden |
| Miscellaneous | Postoperative (gastric surgeries), starvation, autoimmune |

administration of 15–20 g of fast-acting carbohydrate (juice, soda, glucose gel) may be attempted. Glucose levels typically rise in 15 min, at which point a repeat point-of-care (POC) glucose test should be performed with the goal level of ≥ 100 mg/dL. A snack or meal should follow to reduce the risk of recurrence of hypoglycemia. Repeat PO administration of glucose may be performed if the glucose level does not rise appropriately; however, if persistently low, concurrent IV administration of dextrose should be strongly considered [4, 7, 10].

If a patient is lethargic, NPO, or persistently hypoglycemic despite PO glucose administration, parenteral glucose administration should be utilized. Intravenous (IV) administration of dextrose (25 g of 50% dextrose as a bolus commonly available, 10 g of 10% dextrose as a bolus, or 25 g of 10% dextrose over 20 min) or intramuscular (IM) glucagon (1 mg) may be utilized. IV dextrose is preferred if the patient has IV access, since IM glucagon is slower acting [7], may cause transient hyperglycemia [4, 7, 8], and may induce nausea and vomiting, thereby putting patients with AMS at risk of aspiration [4, 7]. POC glucose should be repeated in 15 min. If the glucose level increases appropriately, mental status improves, and the patient can now take PO, the PO method may be revisited and the patient may be provided with a meal in an attempt to prevent recurrence. If hypoglycemia continues to recur and the above conditions are not met, a dextrose infusion should be started [4, 7, 8, 10].

Octreotide may be useful in the setting of persistent hypoglycemia not responsive to other therapies, specifically in the setting of sulfonylurea toxicity. The initial dose of octreotide is 50–75 micrograms (mcg) subcutaneously every 6 h or 50–125 mcg/h IV continuous infusion. For any patient with hypoglycemia, mental status should be monitored and BG measurements should be performed every 15–30 min after glucose administration for 1–2 h and then as needed for persistent hypoglycemia thereafter [4, 8, 11, 12].

It is important to also investigate the underlying etiology and consider the comorbidities in any patient presenting with hypoglycemia. Testing may include CBC with differential, serum electrolytes, liver function tests, toxicologic screening (i.e., alcohol level), urinalysis, cultures, and viral PCR testing. In some cases, advanced endocrinologic evaluation may be warranted, such as thyroid function tests, serum cortisol level, C-peptide, proinsulin, insulin antibodies, and beta-hydroxybutyrate [4, 7]. DM patients with a clear explanation for hypoglycemia related to insulin or sulfonylurea therapy do not routinely require advanced endocrine workup.

The decision on disposition of the ED patient with hypoglycemia is influenced by multiple factors, including PO status, etiology identified or unidentified, transient episode or refractory, risk of recurrence, medication usage, comorbid conditions, and follow-up care. In patients with a transient episode of hypoglycemia who can tolerate PO, the glucose level is readily corrected, the etiology is identified and mitigated, the patient is back to baseline mental status and has access to follow-up care, then discharge may be considered. One may also consider collaborating with the patient's outpatient doctor (primary doctor or endocrinologist) on medication changes, if feasible. For those who are at high risk of recurrence due to prolonged drug action (i.e., patients on sulfonylurea), wherein the etiology of hypoglycemia is

unknown, hypoglycemia is recurrent and/or refractory despite glucose administration, an acute precipitating condition warranting further medical care has been identified, or mental status remains altered, then observation/admission is preferred [4, 7, 8].

Hyperglycemia

Hyperglycemia is a very common condition in the ED and represents a spectrum of presentations from benign to potentially fatal. In patients with uncomplicated presentations of hyperglycemia, evidence-based treatment recommendations based on demonstration of decreased morbidity and mortality are sparse, resulting in a variety of practice approaches to treatment and disposition thresholds of the ED patient. Hyperglycemic emergencies such as DKA and HHS have been well studied and have long been shown to result in significant morbidity and mortality if not appropriately treated. These conditions therefore require rapid identification and intervention to correct the metabolic derangements and to treat the precipitating cause [1, 13, 14]. In the year 2016, 209,000 people were hospitalized in the USA for hyperglycemic crisis, with 180,000 admitted for DKA and 21,000 admitted with HHS (Centers for Disease Control and Prevention, National Diabetes Statistics Report, 2020. Atlanta Ga: Centers for Disease Control and Prevention, US Dept of Health and Human Services; 2020).

Evaluation and Management of Hyperglycemic Crisis

In the ED, the primary goals are rapid evaluation and stabilization. The initial approach to hyperglycemia in the ED begins with obtaining vital signs, a history, and performing a physical exam. Patients with DKA or HHS may present to the ED in a critically ill state, and initial treatment should focus on stabilization and improvement of the patient's hemodynamic status. In a patient with AMS, the primary survey should be performed to evaluate the patient's airway, breathing, and hemodynamics, in conjunction with a POC glucose test and an EKG. Generally, a glucose level >200 mg/dL should trigger further evaluation for the presence of DKA/HHS [1, 7, 13].

Once the resuscitative measures have commenced and the patient stabilizes, a complete history and thorough physical should be performed. It is essential to screen for potential precipitating causes, such as symptoms of stroke, acute coronary syndrome, and infection, as well as symptoms of hyperglycemia and acidosis, such as polyuria, polydipsia, lethargy, abdominal pain, and vomiting. Medication history may also be helpful, as some medications are known to cause hyperglycemia and trigger hyperglycemic emergencies (i.e., steroids, antipsychotics), as well as investigating if insulin is used in their home regimen, and if so, in what formulation

(basal/bolus/pump), what frequency, and when the last doses were administered [1, 7, 13].

On evaluation, particular attention should be paid to signs of shock (tachycardia, hypotension, AMS), acidosis (Kussmaul breathing, tachypnea), dehydration (dry mucous membranes/poor skin turgor), and infection (lung, abdominal, and a thorough skin exam). If an insulin pump is present, inspect the tubing and the pump site for signs of leakage, kinking, or dislodgement [8, 13]. While acidosis in DKA commonly causes abdominal pain and can even mimic an acute abdomen, in HHS, it almost always should be investigated for a precipitating cause. In DKA, if abdominal pain does not improve with the improvement of acidosis, further investigation for a source of the pain should be performed [1, 15].

Recommended lab tests for all patients in which DKA or HHS is suspected include a CBC, chemistry with additional electrolytes (i.e., magnesium and phosphorus), blood gas (venous is sufficient for evaluation of acidosis in the ED [16, 17]), serum osmolality, urinalysis, and a beta-hydroxybutyrate (BHB). Identifying the precipitant is critical, as morbidity is primarily related to the triggering condition. Additional workup may include an EKG (signs of hyperkalemia, ACS), blood and urine cultures (infection), lipase (pancreatitis), troponin, pregnancy test, lactic acid, drug screening, and imaging (stroke, pneumonia, intra-abdominal infection/ischemia) [1, 7, 13].

The initial evaluation and workup for both DKA and HHS are similar, but they are distinct clinical entities. DKA may present as a first manifestation of DM and is more common in people with type 1 DM. The onset is quicker than that of HHS, usually developing within hours to days of the precipitating event. While it can be life threatening, DKA has a lower overall mortality rate (<1%, though higher in the elderly and in patients with concomitant life-threatening illnesses) compared to HHS (5–20%) [1]. The diagnostic criteria for HHS and DKA are listed in Table 11.2.

Table 11.2 Diagnostic criteria for diabetic ketoacidosis and hyperosmolar hyperglycemic state [1, 8, 13, 14]

| | DKA | HHS |
|----------------------------|---|-----------------|
| pH | Mild: 7.25–7.30 Moderate: 7.0–7.24 Severe: <7.0 | >7.30 |
| Serum bicarbonate (mmol/L) | Mild: 15–18 Moderate: 10–15 Severe: <10 | >18 |
| Anion gap (mmol/L) | Mild: >10 Moderate: >12 Severe: >12 | Variable |
| Serum ketones | Present | None or small |
| Urine ketones | Present | None or small |
| Serum osmolality (mOsm/kg) | Variable | Elevated (>320) |
| Glucose (mg/dL) | >250 ^a | >600 |

^aGlucose level may be normal in patients with euglycemic DKA

DKA is usually diagnosed by the presence of hyperglycemia (though initial BG may be variable, it is often less than 500 mg/dL), elevated anion gap metabolic acidosis, and ketonemia. Serum glucose levels are typically much higher in HHS than DKA, often reaching levels of 1000 mg/dL or higher. There is usually not a large anion gap acidosis or ketosis in HHS unless there is another cause such as lactic acidosis, and HHS will have an elevated serum osmolality >320 mOsm/kg [1, 14, 18].

The primary considerations for treatment of DKA and HHS in the ED are careful fluid resuscitation to restore volume and improve perfusion, insulin utilization to reverse ketoacidosis when present, electrolyte management, and treatment of precipitating conditions [1, 7, 13, 14, 18].

IV fluid resuscitation should be rapidly infused in the hemodynamically unstable patient with either of these conditions at approximately 15–20 mL/kg/h for the first 1–2 h. Consideration of hemodynamic improvement, clinical exam changes, measurement of fluid input/output, and lab values are combined to assess perfusion status. Once adequate perfusion is restored, corrected serum sodium levels may be utilized to assess the type of fluid to infuse. Isotonic fluids are usually the initial choice and should be continued while the corrected serum sodium is low, in order to prevent hyponatremia [1, 7, 8, 13, 14]. Normal saline (NS) has been the classic choice; however, studies comparing NS versus balanced crystalloids (Ringer's lactate, plasma-lyte) are emerging suggesting that balanced crystalloid may be preferred, though further investigation is necessary [19–21]. Dextrose should be added to fluids when BG drops to 200–250 mg/dL in a patient who is on an insulin infusion [1, 13, 14].

Insulin therapy is the mainstay of treatment of DKA and may be administered in the form of regular insulin as a continuous infusion or in frequent subcutaneous injections of rapid-acting insulin [1, 13, 14, 22]. In DKA and HHS, IV infusion of regular insulin is often preferred because it is easily titratable with a short half-life. Insulin should only be utilized once adequate fluid resuscitation has been provided and a first set of electrolytes have resulted, specifically, the potassium level [1, 14, 23]. Insulin infusion protocols may vary by institution, though all share the primary aim of decreasing the plasma glucose concentrations at a rate of approximately 50–75 mg/dL/h, usually with a starting dose rate of 0.1–0.14 units/kg/h. Previous recommendations suggested the administration of an initial bolus dose of insulin (0.1 unit/kg) prior to infusion [1], though more recent studies have shown that outcomes are similar in patients who receive both the bolus and infusion and those that only receive infusion [24, 25].

Once the glucose reaches 200 mg/dL in DKA or 300 mg/dL in HHS, the insulin infusion rate may be decreased (0.02–0.05 units/kg/h) and/or dextrose-containing fluids can be added. The rate should be continuously adjusted to maintain glucose levels between 150 and 200 mg/dL in DKA and around 250 mg/dL in HHS until fully resolved, as determined for DKA by closure of the anion gap, normalization of bicarb and pH, and a normal serum osmolality and improvement of mental status for HHS [1, 13, 14]. During the treatment period, POC glucose testing should be performed hourly. BMP and VBG testing should be performed every 2–4 h to guide

therapy decisions and ensure close monitoring of glucose level, electrolyte levels, anion gap, and degree of acidosis, in order to prevent complications that may arise [1, 11, 13]. If the anion gap closes and the acidosis resolves while still in the ED, one dose of subcutaneous long-acting basal insulin may be given, and the insulin infusion may be discontinued 2 h later [1, 7, 13, 14].

Potassium monitoring and replacement in the treatment of DKA and HHS are critical in avoiding life-threatening conditions such as arrhythmia and respiratory muscle weakness [1, 8]. In DKA, total body potassium levels are often decreased, even when the potassium result appears elevated. Parameters have been put forth to guide the treatment algorithm due to the direct relationship that volume expansion, improvement of acidosis, and insulin therapy have on decreasing the potassium level, and they include the goal of maintaining potassium levels at 4–5 meq/L for the duration of treatment. It is recommended to check and wait for the potassium level to result prior to starting insulin therapy. Given the risk of life-threatening arrhythmia with hypokalemia, the current recommendation is to postpone insulin treatment if potassium levels are <3.3 until after potassium supplementation has occurred. If the potassium level is from 3.3 to 5.2, insulin infusion may be started with supplemental potassium (20–30 meq of potassium per liter) added to the IV fluid infusion to prevent severe hypokalemia. If potassium is >5.2, insulin infusion may begin without supplementation [1, 8, 13, 14].

In conjunction with the treatment considerations for DKA/HHS, additional management and therapies targeting the precipitating conditions or comorbidities should be initiated as well. Ultimately, patients with severe DKA or HHS should be admitted to the hospital and managed in an intensive care unit. If the patient clinically improves while undergoing ED treatment, including stabilized vital signs, improving glucose and electrolyte levels, and improvement in the anion gap, then transitioning to a basal/bolus approach and admission to a monitored step-down unit or medical service may be considered [1, 8, 13].

Management of Hyperglycemia in the Absence of a Hyperglycemic Emergency

Once the diagnosis of hyperglycemic crisis has been excluded, there are a wide range of practice approaches to treating hyperglycemia in the ED, due to the paucity of data available to support any particular treatment regimen. Options include no intervention (usually for mild-moderate hyperglycemia), fluid administration, and judicious use of short-acting insulin (usually moderate-severe hyperglycemia) [26–28]. Caution is advised for administering glucose-lowering agents in the ED to patients being discharged if they cannot adequately assess for symptoms of hypoglycemia, unless the patient has been monitored in the ED. Thus far, there are no strong recommendations as to which approach is correct, and there has been no

compelling evidence indicating morbidity or mortality benefits to any particular method.

Limited data suggests that patients who are discharged from the ED with the incidental findings of elevated glucose levels and absence of hyperglycemic emergency are not at an increased risk of short-term adverse events, though these studies did not include patients with type 1 DM or newly diagnosed DM. This highlights that management of these patients should focus on improving long-term glucose management and arranging/ensuring good follow-up, as early treatment of DM decreases long-term morbidity and mortality. The ultimate disposition of these patients varies widely and should take into account patient characteristics and access to outpatient care [26–28].

Elevated random blood sugars are common in the ED setting and, in the absence of a history of DM, are often attributed to stress hyperglycemia. This long-held assumption may not be true. In a large study of ED adult patients without a known history of DM, more than 10% were found to have undiagnosed diabetes based on a gold standard outpatient follow-up 2-h OGTT. The higher the random ED blood sugar, the more likely the presence of undiagnosed diabetes, although diabetes was not uncommon even among patients with random glucose levels as low as the traditional fasting cutoff of 126 mg/dL. This indicates that there should be a high degree of suspicion of chronic dysglycemia when an ED patient has an elevated random blood sugar. Importantly, HbA1c diagnostic testing has been found reliable in the acute care setting. HbA1c testing obtained in acutely ill patients performed similarly to those obtained in the outpatient setting and was not influenced by acute illness [29, 30]. The ED presents a unique opportunity for diagnosing dysglycemia using an HbA1c assay, followed by outpatient referral. We recommend that providers consider obtaining an HbA1c in the acute care setting for those with random glucose levels 126 mg/dL or higher, or at the least provide recommendation for outpatient follow-up DM testing for even modestly elevated random blood sugars.

Type 1 DM (T1D) in the ED

ED patients with T1D should be screened for medication adherence, specifically inquiring as to when the last dose of basal insulin was administered. Missing or delaying even one dose of basal insulin can put these patients at risk for rapid deterioration to severe hyperglycemia and/or DKA while they are in the ED and not taking their usual home medications. This screening should occur even if the original glucose level is normal and the patient is present for an unrelated concern. It is essential to screen for the presence of an insulin pump which, if present, should be inspected to ensure that it is properly placed and functioning. If a dose of basal insulin was missed or an insulin pump is dislodged or not functioning, basal insulin should be immediately administered. The dose administered may be determined using a weight-based calculation of 0.2 units/kg or based on the patient's home dose.

Diabetes Management in the Emergency Department Observation Unit (EDOU)

Introduction

The EDOU is a 24–48-h short-stay unit designed for an extended ED stay and has been increasingly utilized in hospitals nationwide [31]. Patients are assigned for observation care when a brief ED visit is insufficient for evaluation and management, but criteria for full inpatient admission are not met. The EDOU is typically adjacent to the main ED and staffed by ED providers and nurses. Use of the EDOU has been associated with many benefits, including enhanced care, reduced length of stay, improved ED throughput, and decreased cost [31, 32]. The EDOU structure and timing allow for multiple consultations, if needed, as well as care coordination [32]. Given the relatively lower acuity of the EDOU patient population, protocols and algorithms are frequently utilized to streamline care for a variety of diagnoses. Greater than one-third of US hospitals have a dedicated EDOU [33], with over 2.3 million annual visits in the USA [33, 34].

DM has been increasingly recognized as one of the many conditions suitable for management in the EDOU setting. Hyperglycemia and hypoglycemia may be appropriately managed within the confines and time course of the EDOU setting. Patients presenting to the ED for other conditions may also be noted as having significantly uncontrolled DM, both newly and previously diagnosed, and as being in need of medication adjustment.

Hemoglobin A1c (HbA1C) Use in the EDOU

The United States Preventive Services Task Force recommends DM screening for adults aged 35–70 who are overweight or obese [35], while the American Diabetes Association recommends screening all adults aged 35+ as well as any adult who is overweight or obese, combined with another risk factor [36]. Despite the above guidelines, rates of undiagnosed DM and prediabetes in the USA are accelerating. A multitude of factors may contribute to this problem, including socioeconomic factors, such as lack of insurance or access to routine preventative healthcare. Earlier detection of DM, reducing the time between disease onset and clinical diagnosis, could have significant benefit for patients, mitigating the accumulation of complications as well as economic burden on the healthcare system. Earlier DM diagnosis is associated with reduction in risk of cardiovascular outcomes, renal disease, retinopathy, and all-cause mortality [37, 38].

For some patients, the ED visit presents as an opportunity for screening that may not otherwise occur soon or at all in the community. HbA1c has been shown to be a reliable indicator of long-term glycemia in the ED, including new diagnosis of DM and pre-DM, known to be prevalent in the ED [29].

Given the increasing utilization of the EDOU in hospitals and the extended time frame for patient stay, the EDOU provides a novel and rich environment for HbA1c screening given the high frequency of undiagnosed dysglycemia in this patient population. Silverman et al. [39] describe a performance improvement project at a tertiary care center in New York, in which patients without known DM or pre-DM were offered HbA1c testing while in the EDOU. No additional blood draw was needed, as prior samples drawn in the ED were utilized for testing. Among 256 EDOU patients, 9% were found with newly diagnosed diabetes and 52% newly diagnosed prediabetes [39]. While higher rates were found in ages ≥ 45 , patients in all adult age groups commonly tested positive for dysglycemia, and therefore universal screening with HbA1c testing should be considered for standard care in all EDOUs.

Sop et al. performed a retrospective screening study in the EDOU in West Virginia, among patients without prior diagnosis of DM, using fasting BG; 27.8% of patients had a glucose level ≥ 126 mg/dL indicative of possible DM, and 21.2% had pre-DM range glucose levels [40]. One limitation of this study is the component of stress hyperglycemia that could be present for the EDOU patient and temporarily raise glucose levels. HbA1c is beneficial, in that short-term fluctuations in glucose are less likely to have a major effect on skewing levels.

HbA1c measurement in the EDOU for patients with known DM and/or hyperglycemia can also be of great utility, offering the opportunity for intervention during an EDOU stay. Patients manifesting a severely elevated HbA1c $\geq 10\%$ have significantly higher odds of having a DM-related hospitalization compared with HbA1c $< 7\%$ (odds ratio = 2.13, 9% confidence interval = 1.36–3.33) [41]. Further, the knowledge of poorly controlled DM can help guide acute and long-term care such as outpatient medication modification and referrals.

Hyperglycemia Management in the EDOU

The EDOU provides a fitting environment for management of routine hyperglycemia, in the absence of DKA, HHS, or other reasons requiring hospital admission. Ordering of HbA1c is highly recommended in this scenario to help with medical decision-making, as patients may or may not report a known DM history [42]. Insulin dosing algorithms can be used for short-term management of hyperglycemia in the EDOU with high rates of discharge and low rates of readmission [43, 44]. A simple weight-based basal and bolus insulin regimen, such as 0.4 units/kg total daily dose (split into 50% basal and 50% bolus), can be used to estimate insulin doses by EDOU staff to begin therapy even before the arrival of an endocrine consultant.

For newly diagnosed diabetes patients found to have an HbA1c of 6.5–8.9%, discharge on metformin should be considered along with the provision of patient education and outpatient follow-up. For patients with known diabetes but poorly controlled HbA1c, diabetes discharge medication regimens can be modified based

on the HbA1c level, and for those with severely elevated HbA1c ($\geq 9.0\%$) EDOU, endocrine consultation can be considered (see Endocrinology Consult in the EDOU below).

Hypoglycemia Management in the EDOU

Hypoglycemia events with an uncomplicated etiology are suitable for management in the EDOU. Accidental over-administration of insulin or sulfonylurea, or used with inadequate carbohydrate ingestion, can precipitate hypoglycemia. The EDOU presents a useful setting for withholding of additional hypoglycemic agents, close monitoring of BG, offering of food intake, and, if needed, administration of intravenous dextrose fluids, until the medication effect has waned [42]. The 24–48-h EDOU time frame allows for adequate time to correct the hypoglycemia but also the opportunity for endocrine consultation for medication management. Oftentimes, the sulfonylurea agent may be discontinued and replaced (if needed) with an alternate drug with less risk for hypoglycemia. Patients using insulin can have the doses adjusted to help maintain glucose in safer ranges.

Endocrinology Consult in the EDOU

Wait times for a new endocrinology appointment can be prolonged in some areas, given a relative lack of endocrinologists compared to the increasing need for appointments, with delay often greater than 3–6 months [45]. The EDOU presents a useful setting for sooner intervention for patients identified with high HbA1c, providing enough time during the stay for HbA1c assessment, DM education, and endocrinology consult at many centers. Schulman-Rosenbaum et al. described a quality improvement program combining HbA1c screening and standardized endocrinology consultation for patients identified with HbA1c $\geq 9\%$ [46]. Among 190 patients with consult performed, 92.1% had diabetes medication adjustments, including many with new prescriptions for injectable therapies. Importantly, such a program relies on the collaboration of the inpatient diabetes team with the ED staff. The time course of the EDOU stay is sufficient for the consult to occur and allows treatments to be initiated much sooner than outpatient referral. Figure 11.1 outlines a suggested simplified approach to HbA1c results for the EDOU staff.

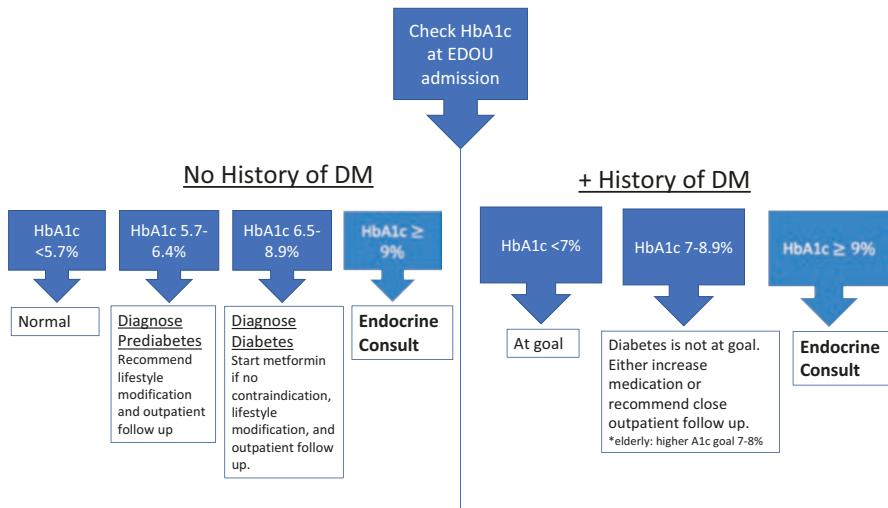


Fig. 11.1 Suggested approach for interpretation of HbA1c screening results in the Emergency Department Observation Unit (EDOU), for patients with and without a history of Diabetes Mellitus (DM) (adapted from Schulman-Rosenbaum et al. [46])

Transition to Outpatient

Discharge from the EDOU for patients with newly diagnosed DM, or starting new therapies for DM management, requires bedside education of glucometer and, in some cases, insulin self-administration. Coordination with the outpatient pharmacy to ensure that prescriptions are covered by the patient's insurance company is recommended. Referral for outpatient follow-up with primary care and/or endocrinology would be advised to ensure adequate transition to the outpatient setting.

Conclusion

DM-related emergencies are a common presentation to the emergency department, and it is therefore essential for the ED provider to promptly recognize and initiate treatment for conditions such as hypoglycemia, DKA, and HHS, as described in this chapter. The EDOU serves as a useful setting to treat patients with uncontrolled or undiagnosed DM in the absence of a DM-related emergency and should be considered in order to provide further DM management in collaboration with the endocrinology team.

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Chapter 12

Inpatient Glucocorticoid-Induced Hyperglycemia



Elizabeth Paul and Danielle Brooks

Introduction

Glucocorticoids are utilized in the treatment of numerous acute and chronic conditions, inflammatory states, and autoimmune diseases. Despite their usefulness and effectiveness, glucocorticoids are frequently associated with serious adverse effects including fluid retention, hypertension, avascular necrosis, adrenal suppression, mood disorders, and glucocorticoid-induced hyperglycemia [1].

Glucocorticoid-Induced Hyperglycemia

Glucocorticoid therapy remains a mainstay of treatment for many diseases, and as a result, glucocorticoid-induced hyperglycemia is a frequently encountered adverse side effect. This creates a challenge in diabetes management, especially in the inpatient setting where optimal glucose control has been linked with overall improved patient outcomes [2]. Glucocorticoid-induced hyperglycemia is an abnormal elevation in blood glucose levels seen in the presence of glucocorticoids; the desirable range for blood glucose levels in hospitalized patients is typically between 100 and 180 mg/dL. Glucocorticoid-induced hyperglycemia is commonly seen in patients with existing diabetes or prediabetes or can occur in patients without a prior history of impaired glucose metabolism. In such patients, chronic or frequent use of glucocorticoids can lead to the development of overt diabetes [3]. It may be confusing for

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an inpatient team to determine the exact type of diabetes if the team is not familiar with the patient's medical history, if the patient is a poor historian, or if they have infrequent outpatient follow-up. In these circumstances, it is often difficult to distinguish if a patient has type 2 diabetes versus glucocorticoid-induced diabetes; however, the pathogenesis of the two conditions is distinct [4]. As opposed to the development of insulin resistance and progressive pancreatic beta-cell impairment in type 2 diabetes, glucocorticoid-induced diabetes is largely due to pancreatic alpha-cell hyperplasia and increased gluconeogenesis from the liver after exposure to glucocorticoids [4]. While there is limited practical guidance on inpatient management of glucocorticoid-induced hyperglycemia, a better understanding of this challenging clinical entity can aid in improved glucose control, thereby improving patient outcomes.

Epidemiology

The incidence of glucocorticoid-induced hyperglycemia ranges anywhere between 12 and 32% with variability attributed to indication, duration of therapy, and dose of glucocorticoids used [3, 5–8]. Other patient-specific factors such as age, body mass index (BMI), and personal and family history of diabetes can also contribute to an individual's chance of developing glucocorticoid-induced hyperglycemia [9]. Observational data has shown that glucocorticoids are linked to 2% of incident diabetes cases in a primary care population, and the odds ratio for presenting with new-onset diabetes following glucocorticoid exposure ranges from 1.5 to 2.5. Glucocorticoid-induced hyperglycemia developed in 32.3% of patients without a history of diabetes that were given systemic glucocorticoids. In another 18.6%, diabetes persisted during follow-up [10]. The incidence of glucocorticoid-induced diabetes, diabetes which develops secondary to glucocorticoid use in individuals without a prior history of diabetes, is estimated to range between 15 and 40%. This entity may resolve after cessation of glucocorticoid use but can also persist with long-term glucocorticoid use [11].

One can infer that the use of glucocorticoids may be unmasking an underlying impairment of glucose metabolism since glucocorticoid-induced hyperglycemia is generally considered to be a temporary adverse effect that is expected to resolve once the glucocorticoid effect is no longer present. Pre-screening with measurements of fasting serum glucose levels and hemoglobin a1c (HbA1c) prior to initiation of glucocorticoids or referring to prior results and records may be helpful in distinguishing this entity from preexisting prediabetes or type 2 diabetes.

Common Indications for Glucocorticoids

Glucocorticoids are synthetic analogs of the natural glucocorticoid hormones produced by the adrenal cortex [1]. The glucocorticoid and mineralocorticoid activities of the synthetic hormones vary in intensity. Glucocorticoids, such as hydrocortisone, prednisone, methylprednisolone, and dexamethasone, have many different effects on nearly all cells within the body. Glucocorticoids are vital for life; they are involved in the regulation of metabolism, immune function, and even neurophysiology [12]. Glucocorticoids in the hospital are often utilized at supraphysiologic doses for their immunosuppressive, anti-inflammatory, and vasoconstrictive properties. Some common indications for inpatient use of glucocorticoids that one may encounter include pulmonary disease, COVID-19 infections, neurological illnesses, hematologic disorders, dermatologic conditions, allergic reactions, autoimmune diseases, prevention of organ transplant rejection, endocrine disorders, and shock [5, 13, 14].

Morbidity and Mortality of Glucocorticoid-Induced Hyperglycemia

Hyperglycemia in hospitalized patients has been associated with increased length of stay, increased frequency of emergency department visits, greater risk of admission to critical care units, higher risk of infections, slower wound healing, and mortality [15]. Despite its prevalence, there is scant data available on patient morbidity and mortality outcomes, specifically with glucocorticoid-induced hyperglycemia in inpatient settings.

Diabetes mellitus is also a known risk factor for the development of macrovascular and microvascular complications. As a result, it is proposed that concurrently having inflammatory conditions and glucocorticoid-induced hyperglycemia may result in worsened cardiovascular outcomes and increased mortality. Rheumatologic diseases, a common indication for glucocorticoid therapy, are associated with higher mortality in patients experiencing glucocorticoid-induced hyperglycemia. This association may be primarily attributed to the increased cardiovascular risk linked to these disorders [15–17]. Fluctuations in glucose levels contribute to increased low-density lipoprotein (LDL) cholesterol, endothelial dysfunction, activation of the coagulation cascade, increased production of pro-inflammatory cytokines, and oxidative stress, which can lead to the progression of macrovascular disease and higher cardiovascular mortality [15].

In a retrospective observational study of 2,424 patients, mortality, cardiovascular events, and infections were notably higher in patients with glucocorticoid-induced hyperglycemia compared with those that were euglycemic. This study also found that the risk for hypoglycemia was also twofold higher in patients on glucocorticoids. The increased rate of the observed adverse effects with

glucocorticoid-induced hyperglycemia was noted to be independent of a preexisting diagnosis of diabetes [18].

Glucocorticoid-induced hyperglycemia is also a major predictor of graft failure in renal transplant patient populations, associated with a 2–3 times higher risk of fatal and nonfatal cardiovascular events when compared to transplant patients without diabetes [15]. In addition, hyperglycemia in the setting of glucocorticoid use can lead to diabetic ketoacidosis and hyperglycemic hyperosmolar states, necessitating prolonged and/or repeated hospital admissions for aggressive hydration and insulin therapy, as well as an increase in complications from inpatient hyperglycemia [5, 15].

Glucocorticoids and COVID-19

Although there have been great advancements in treatment approaches and patient outcomes, SARS-CoV-2 infections (COVID-19) continue to be a significant health concern throughout the world. In cases of severe COVID-19 infections in which patients require oxygen therapy or mechanical ventilation, glucocorticoids, particularly dexamethasone, remain a mainstay of treatment [14, 19]. While dexamethasone has been lifesaving for many with COVID-19 infections, it has also led to challenges in clinical management, especially in terms of glucocorticoid-induced hyperglycemia. Achieving blood glucose control in patients with COVID-19 is crucial to improving recovery rates from acute infection and reducing mortality [20]. Glucocorticoids in COVID-19 infections can raise blood sugar levels in several ways through inherent glucocorticoid effects and through elevated levels of inflammatory cytokines, which can lead to insulin resistance. Therefore, in patients with COVID-19, it is essential to closely monitor blood glucose levels, especially when dexamethasone is used [20]. Further details regarding inpatient glycemic management in COVID-19 can be found in Chap. 13.

Mechanisms of Glucocorticoid-Induced Hyperglycemia

Glucocorticoids can induce hyperglycemia through several mechanisms involving the liver, adipose tissue, skeletal muscle, gut, and pancreatic alpha and beta cells as illustrated in Fig. 12.1. In the liver, glucocorticoids activate enzymes involved in carbohydrate metabolism, including phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6P), which promote gluconeogenesis [21]. Glucocorticoids oppose the effects of insulin on the liver, which contributes to increased hyperglycemia, hepatosteatosis, and insulin resistance. In the fasted state, the liver maintains euglycemia through gluconeogenesis and glycogenolysis. After eating, these processes are counteracted or suppressed by insulin in order to maintain euglycemia [15]. Physiologic insulin action in the liver leads to decreased

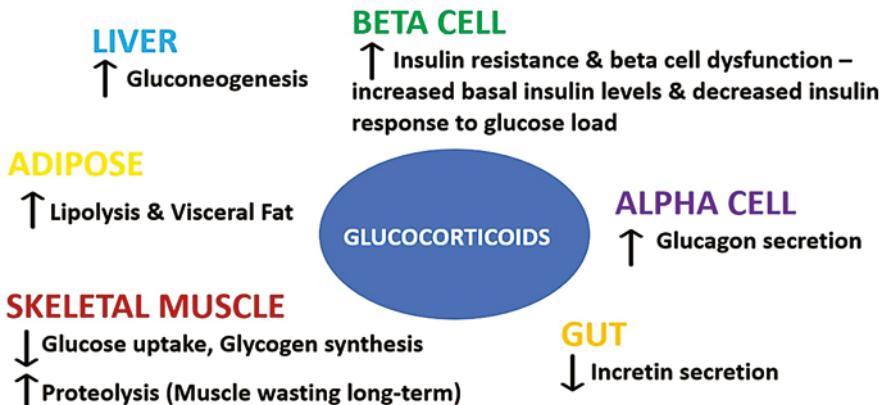


Fig. 12.1 Mechanisms of glucocorticoid-induced hyperglycemia [21, 22]

hepatic glucose production in the liver (through inhibition of gluconeogenesis and glycogenolysis) and promotes increased glucose utilization and storage [21].

Skeletal muscles are major sites of insulin-stimulated glucose uptake, glucose utilization, and glycogen synthesis. Glucocorticoids lead to proteolysis and break down glycogen stores in skeletal muscles. Proteolysis disrupts insulin signaling for glucose uptake in skeletal muscle cells, and the amino acids from the degradation of proteins go on to become substrates for hepatic glucose production [15, 21].

In adipose tissue, glucocorticoids lead to both an increase in visceral fat and lipolysis. Glucocorticoid-related pro-adipogenic effects are thought to be mediated by increased genetic expression of pathways that maximize insulin effects, which lead to increased deposition of abdominal adipose tissue, reduced glucose tolerance, and elevations in triglyceride levels. In addition, glucocorticoids can reduce adiponectin levels which are related to insulin sensitivity and decrease serum tumor necrosis factor-alpha (TNF- α) levels involved in insulin resistance. The lipolytic effect of glucocorticoids is due to the upregulation of transcription factors that increase the activity of lipases, which are more pronounced in peripheral tissues [22].

The effect of glucocorticoids on pancreatic beta cells and alpha cells contributes to hyperglycemia as well. Glucocorticoids cause beta cell dysfunction through several molecular mechanisms ultimately leading to insulin resistance. In alpha cells, increased secretion of glucagon leads to glucocorticoid-induced hyperglycemia [21, 22]. Glucocorticoids also lead to decreased insulin secretion in response to glucose loads in the gut after eating by inhibiting the effect of incretins [22]. Incretin-based drugs may be beneficial in targeting this mechanism of glucocorticoid-induced hyperglycemia and are discussed later in this chapter.

Comparison of Commonly Used Glucocorticoids in Inpatient Settings

Endogenous glucocorticoids, produced in the adrenal gland, are synthesized from cholesterol and are physiologically released according to circadian and pulsatile ultradian rhythms. Typically, 8–15 mg/dL of endogenous glucocorticoids are present at any given time, 90% of which is protein bound while the other 10% is free [15]. While similar in their mechanisms of action within the body, the doses of exogenous glucocorticoids that are used and their individual pharmacokinetic properties differ from that of endogenous glucocorticoids. The exogenous glucocorticoids that are commonly encountered in inpatient settings include hydrocortisone, prednisone, methylprednisolone, and dexamethasone. Table 12.1 provides a comparison of these four commonly encountered glucocorticoids.

Hydrocortisone is a short-acting glucocorticoid with a duration of action of 8–12 h; the hyperglycemic effects with hydrocortisone can be seen within 1 h of administration and can last for around 6 h. Prednisone and methylprednisolone are both intermediate-acting glucocorticoids with a duration of action of 12–36 h; the hyperglycemic effects for both intermediate-acting glucocorticoids are typically seen 4 h after administration. Glucocorticoid-induced hyperglycemia can persist for 16 h after administration of the last dose [3, 23, 24]. When given as a single daily dose earlier in the day, both short-acting and intermediate-acting glucocorticoids may not impact fasting blood glucose levels. However, they can be expected to cause hyperglycemia from midday until the evening. This is not the case with multiple daily doses of short- and intermediate-acting glucocorticoids or with even a single dose of a long-acting glucocorticoid such as dexamethasone [15]. The duration of action for dexamethasone is between 36 and 72 h, and the hyperglycemic effects can last up to 72 h after the last dose of dexamethasone [3, 23, 24]. The pharmacokinetics of glucocorticoids is important to understand in order to monitor and treat glucocorticoid-induced hyperglycemia optimally.

Table 12.1 Comparison of commonly used glucocorticoids in inpatient settings [3, 23, 24]

| Commonly used glucocorticoids in inpatient settings | Equivalent dose (mg) | Potency (relative to hydrocortisone) | Duration of action (hours) | Hyperglycemic effects: time to onset > peak > resolution (h) | | |
|---|----------------------|--------------------------------------|-----------------------------|--|----------|-------|
| Hydrocortisone | 20 | 1 | 8–12 (short-acting) | 1 | 3 | 6 |
| Prednisone | 5 | 4 | 12–36 (intermediate-acting) | 4 | 8 | 12–16 |
| Methylprednisolone | 4 | 5 | 12–36 (intermediate-acting) | 4 | 8 | 12–16 |
| Dexamethasone | 0.75 | 30 | 36–72 (long-acting) | 8 | Variable | 24–72 |

Detection and Monitoring of Glucocorticoid-Induced Hyperglycemia

There are no specific diagnostic criteria or target treatment goals established for glucocorticoid-induced hyperglycemia. This may hinder detection of this entity, especially in situations where clinicians are not actively monitoring patients for the development of hyperglycemia in the presence of glucocorticoids. The same thresholds for hyperglycemia that are used in the diagnosis of diabetes mellitus are often also used for glucocorticoid-induced hyperglycemia. These criteria are met when there is a fasting glucose level greater than or equal to 126 mg/dL, a glucose level greater than 200 mg/dL 2 h after a 75 g oral glucose tolerance test, a random blood glucose level greater than 200 mg/dL, or HbA1c $\geq 6.5\%$ [25]. Detection and diagnosis of glucocorticoid-induced hyperglycemia remain challenging due to the pattern of the hyperglycemic effect observed with glucocorticoids.

Glucocorticoids generally impact postprandial blood glucose levels much more significantly than fasting blood glucose levels. In many circumstances, such as with the use of short- or intermediate-acting glucocorticoids in single morning doses, fasting blood sugar levels may be within the normal range [3, 5]. In patients without a preexisting diagnosis of diabetes mellitus, point-of-care finger-stick blood glucose monitoring is not routinely done; there may only be a fasting serum glucose level from a blood chemistry panel checked as a part of routine morning labs. In these patients with seemingly “normal” glucose levels in the morning, hyperglycemia may not be present until after glucose exposure or until later in the day when the diabetogenic effect of glucocorticoids is present [3].

The use of continuous blood glucose monitors in patients with chronic obstructive pulmonary disease in a cross-sectional study revealed that glucocorticoid-induced hyperglycemia was predominantly noted in the afternoon and evening times [26]. The detection of postprandial hyperglycemia after lunch is also highly specific for glucocorticoid-induced hyperglycemia [5]. Therefore, the general recommendation is to use capillary blood glucose monitoring before meals and at bedtime starting at the time of glucocorticoid initiation for patients with established diabetes and patients with risk factors for diabetes (i.e., high BMI, advanced age, family history of diabetes, or prediabetes) [3, 15]. Capillary blood glucose monitoring can be discontinued after 48 h if patients remain euglycemic during this time period, as nearly 94% of the cases of glucocorticoid-induced hyperglycemia develop within 1–2 days of glucocorticoid initiation [15]. For those patients with glucocorticoid-induced hyperglycemia, monitoring of blood glucose levels should continue until resolution of hyperglycemia or at least until cessation of glucocorticoid therapy in patients without preexisting diagnosis of diabetes.

While it may be helpful to assess HbA1c levels prior to the initiation of glucocorticoids to identify preexisting diabetes or prediabetes, HbA1c is not sufficient for detection or diagnosis of glucocorticoid-induced hyperglycemia, especially in inpatient settings. This is because HbA1c reflects glycemic control in the weeks or months prior rather than the resultant hyperglycemia associated with more acute

glucocorticoid use. Furthermore, in inpatient settings, glucocorticoids are often used in patients with other underlying conditions that may affect the reliability of HbA1c measurements such as chronic kidney disease, hemoglobinopathies, or liver disease [3].

Management of Glucocorticoid-Induced Hyperglycemia

There are no established guidelines to guide the management of glucocorticoid-induced hyperglycemia in hospitalized patients. Rather, there are opinion-based guidance documents based on limited randomized controlled trial data, so the best treatment is unclear [27]. In the inpatient setting, insulin is generally the preferred therapeutic agent to achieve glycemic control, both in insulin-naïve patients without diabetes and in their counterparts when blood glucose levels exceed 140 mg/dL [15, 25]. Prior studies have reviewed various strategies and combinations of insulin formulations used in the management of glucocorticoid-induced hyperglycemia. Many of these studies are limited due to small sample sizes, short study durations, inconsistent terminology, varying protocols, and suboptimal glucose control [27]. Here, we will discuss some practical therapeutic strategies that are often employed in clinical practice to achieve better glycemic control in the setting of glucocorticoids.

One such strategy involves using a high-dose weight-based basal-bolus insulin (BBI) regimen, starting at 0.5–0.6 units/kg body weight, distributing 30–40% of this total daily dose (TDD) as basal insulin administered once daily, and the remaining 60–70% of the TDD as bolus insulin administered prior to meals [27]. The goal of this strategy is to target the disproportionate increase in postprandial blood glucose levels that is seen with glucocorticoids while maintaining euglycemia even in the setting of increased fasting hyperglycemia. In conjunction with this insulin distribution, a more liberal insulin correctional scale is utilized (i.e., ISF 1:25 for glucose ≥ 150 mg/dL). This regimen is often only a starting point, and further titration is required. Total daily requirements should be calculated, including both the standing insulin and correctional doses, and then insulin doses should be redistributed again using similar ratios.

In patients who do not have fasting hyperglycemia, it may be possible to manage glucocorticoid-induced hyperglycemia with a premeal bolus insulin regimen alone, especially in cases where short-acting glucocorticoids such as hydrocortisone are used [3]. Rapid-acting insulins such as insulin lispro can be started at a dose of 0.1 units/kg per meal along with premeal correctional scales. This starting dose can be titrated based upon daily utilization of correctional insulin to achieve adequate glycemic control. Another option for titration is to increase premeal bolus insulin doses in increments of 0.04 units/kg per meal if preprandial glucose levels are between 200 and 300 mg/dL or in increments of 0.08 units/kg if preprandial glucose levels are greater than 300 mg/dL [15].

An alternative therapeutic strategy involves insulin regimens with neutral protamine Hagedorn (NPH) insulin. Prior studies have demonstrated the effectiveness of NPH for achieving glycemic control in glucocorticoid-induced hyperglycemia. The pharmacokinetics of NPH aligns more with the hyperglycemic effect observed in the setting of glucocorticoids. The peak time and the duration of action of NPH are similar to those of commonly used intermediate-acting glucocorticoids such as prednisone [28]. Given this similarity in pharmacokinetics, patients that are on single daily glucocorticoid doses may benefit from an NPH once-daily regimen using an initial dose of 0.4 units/kg [10]. Single daily glucocorticoid dose and NPH dose in this circumstance should be timed to be administered together for optimal results.

For patients who are on multiple glucocorticoid doses daily or long-acting glucocorticoids such as dexamethasone, NPH insulin alone will not be sufficient to achieve adequate glycemic control. In these cases, twice-daily NPH dosing and/or addition of premeal bolus insulin should be considered. Umpierrez et al. recommend that the TDD of insulin can be divided into a distribution of 30% NPH insulin and 70% premeal bolus insulin divided equally for three premeal doses [29]. Per the systematic review of glucocorticoid-induced hyperglycemia by Brooks et al. the insulin regimen with the greatest likelihood of effectiveness was demonstrated in studies using BBI with NPH. The authors in this review recommend using BBI with TDD of 0.5 units/kg with the addition of NPH insulin each morning using either 0.5 units/mg of prednisone equivalent or 0.1–0.4 units/kg according to prednisone 10 mg dose increments (i.e., 0.1 units/kg per prednisone 10 mg used) [27]. For those patients with severe hyperglycemia that are not controlled with a subcutaneous insulin regimen, an insulin infusion should also be considered [15].

Body weight is a key component in the strategies of subcutaneous insulin dosing for glucocorticoid-induced hyperglycemia described above. However, estimated insulin doses using body weight alone will likely not be sufficient to achieve adequate glycemic control [30]. A prospective study by Chen et al. evaluated the clinical variables and associations between daily insulin requirements in hospitalized adults with and without type 2 diabetes who were taking at least 20 mg/day of prednisolone. The patients involved in this study were managed with an insulin infusion, titrated to achieve a mean glucose of 145 mg/dL. Body weight accounted for only 11% of the variability observed. Instead, it was found that 54% of the variability in total daily insulin requirements depended upon a patient's sex, HbA1c, diabetes status, and diabetes medications that they had been on prior to hospitalization [30]. Incorporation of these other variables, along with body weight, when strategizing insulin dosing for patients with glucocorticoid-induced hyperglycemia may prove to be useful [30, 31]. Regardless of the insulin regimen utilized, a cautious approach should be taken with insulin titration, especially with glucocorticoid dose increases and tapers.

There are several limitations when it comes to utilizing oral hypoglycemic agents for the management of glucocorticoid-induced hyperglycemia in hospitalized patients. On their own, oral agents may not provide sufficient glycemic control. Insulin sensitizers such as metformin and pioglitazone theoretically may be beneficial in the treatment of glucocorticoid-induced hyperglycemia, but in inpatient

settings, the use of these agents is limited among acutely ill patients who are at risk for kidney injury, hypoxia, and other hospital-acquired complications. In addition, while beneficial in reducing insulin resistance, these agents do not acutely lower glucose levels. Insulin secretagogues, such as sulfonylureas and meglitinides, are avoided in hospitalized patients due to their increased risk for hypoglycemia while acutely ill with altered daily routines and variable nutritional intake [3, 5].

Incretin-based drugs are more favorable for the management of glucocorticoid-induced hyperglycemia as they largely affect postprandial hyperglycemia and have milder side effect profiles. Even then, gastrointestinal side effects are commonly encountered with initiation of long-acting GLP-1 agonists, limiting their use among acutely ill hospitalized patients. Their use in the hospital setting has not been well studied. The glucose-lowering effects of DPP4 inhibitors may also not be sufficient in managing glucocorticoid-induced hyperglycemia when long-acting, high-dose, or long-duration glucocorticoids are required. There may be a role for DPP4 inhibitors as adjunctive therapy in these situations, and their use may be beneficial in achieving glycemic control while reducing insulin requirements, especially when preparing for discharge [3, 5]. Several additional resources for the management of glucocorticoid-induced hyperglycemia can be found in Chap. 24—Diabetes and Oncology.

Practical Guidance with Glucocorticoid Dose Adjustments and Transition to Outpatient Care

Glucocorticoid therapy initiated in the hospital is often continued upon discharge and frequently involves future dosage tapers. This adds another layer of complexity to the management of glucocorticoid-induced hyperglycemia. Prior to discharge on glucocorticoids, all patients should be educated on glucocorticoid-induced hyperglycemia as well as glucose targets, hypoglycemia risk, and hyperglycemia. Patients that are new to self-management of hyperglycemia will require education on glucometer use and insulin administration as well as nutritional counseling. Earlier anticipation of discharge glucocorticoid needs will be beneficial to ensuring that patients are adequately prepared for self-management of glucocorticoid-induced hyperglycemia at home and may prevent discharge delays.

It may be beneficial to provide patients with an individualized treatment regimen with glucose targets and schemes for adjustment if they are being discharged on a prolonged glucocorticoid course. Furthermore, attention should be paid to the duration of glucocorticoid use and presence of a steroid taper after discharge, which can impact the appropriate dose of insulin. For example, a patient's insulin regimen may need to be discontinued or lowered at the time of completing the glucocorticoid course. In some cases, patients may be given an insulin taper to accompany the steroid taper, with both doses reducing in tandem (e.g., reducing insulin dose(s) by 10–20% with each steroid decrease). For patients with a limited ability to

understand complex dosing recommendations, a lower dose of insulin can be used at discharge to account for decreasing requirements over the course of the steroid taper. Patients should also have access to glucose monitoring equipment at home, and self-monitoring of blood glucose levels should continue in the outpatient setting for at least the duration of glucocorticoid therapy. Close outpatient follow-up with primary care and/or endocrinology should also be arranged in case of difficulty with glycemic control or unforeseen changes to glucocorticoid dosing. All patients should have HbA1c levels checked every 3 months while on glucocorticoids [3].

Conclusion

Glucocorticoid-induced hyperglycemia is a challenging concept in inpatient endocrinology management especially due to the lack of clear treatment guidelines. Nonetheless, maintaining euglycemia is of vital importance in the inpatient setting. Several strategic approaches that may prove useful were discussed in this chapter including high-dose weight-based BBI regimen, premeal bolus insulin regimens, NPH-based regimens, and oral hypoglycemic agents. Regardless of the method utilized, an individualized and cautious approach is recommended in the management of glucocorticoid-induced hyperglycemia for all patients.

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Chapter 13

Diabetes and COVID-19



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Abbreviations

| | |
|---------------|--|
| CDC | Centers for Disease Control and Prevention |
| CGM | Continuous glucose monitoring |
| DPP-4 | Dipeptidyl Peptidase-4 |
| FDA | Food and Drug Administration |
| HbA1c | Hemoglobin A1c |
| IL | Interleukin |
| IRS-1 | Insulin receptor substrate 1 |
| POC | Point-of-care |
| TNF- α | Tumor Necrosis Factor-alpha |

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Introduction: Impact of COVID-19 on Diabetes

First identified as the cause of an outbreak of an atypical pneumonia-like illness in Wuhan, China in mid-December 2019, the SARS-CoV-2 virus would soon become the cause of the COVID-19 global pandemic the likes of which had not been seen in nearly a century. In June 2020, the Centers for Disease Control and Prevention listed comorbid conditions associated with more severe illness, diabetes mellitus being notable among them. In the early days of the pandemic, it was quickly realized that COVID-19 patients were presenting with unusually high blood glucose levels and many presenting with diabetes-related ketoacidosis (DKA) even in the absence of type 1 diabetes. This started an ongoing debate about whether it was the virus itself leading to hyperglycemia or hyperglycemia predisposing to more severe disease.

Bidirectional Relationship of COVID-19 and Diabetes

Since then, numerous studies have backed this finding that patients with diabetes have higher COVID-19 morbidity (demonstrated by increased need for mechanical ventilation, admission to intensive care unit) and mortality [1–4], whether preexisting or newly diagnosed at the time of COVID-19 infection. Zhang et al. [5] found that patients with diabetes and hyperglycemia were at a 2.5 times higher risk of severe COVID-19 infections compared to patients without diabetes but with hyperglycemia. Other studies have shown that patients with hyperglycemia who are treated with anti-hyperglycemic agents during COVID-19 infection have lower mortality [6] suggesting that hyperglycemia could impair immune response to acute infection.

Infection itself poses challenges to glycemic control during the acute stage but also during recovery and potentially “long-COVID” stages of disease [7]. Preliminary studies demonstrated patients with COVID-19 had greater prevalence of hyperglycemia [8, 9] among hospitalized patients with COVID-19 than those without (56.6% vs 38–40%). This was theorized to be secondary to the presence of high levels of pro-inflammatory cytokines during acute infection leading to insulin resistance +/- beta-cell dysfunction [10]. Superimposed on the inflammatory response are the impact of the drugs used to treat COVID-19 including glucocorticoids which are notorious for causing hyperglycemia.

COVID-19 and Diabetes Mellitus: Pathophysiology

COVID-19 infection is associated with worsening hyperglycemia in persons with and without diabetes [11, 12]. Hyperglycemia is mediated by direct viral effects and a pro-inflammatory state, generated by the cytotoxic/cytokine response to infection.

The impact on glucose homeostasis is typically acute; recent reports have also noted extended hyperglycemia duration in infected patients and increased incidence of diabetes in the population during the COVID-19 pandemic [10, 11] (Table 13.1).

SARS-CoV-2 viral infection and replication in metabolic tissues (liver, adipose tissue, and liver) promotes an integrated stress response, activating serine kinases, resulting in post-insulin receptor dysfunction, increased reactive oxygen species generation, endoplasmic reticulum stress, altered adipokine secretion [13–15]. SARS-CoV-2 infection increases the production of myeloperoxidase, promoting insulin resistance [16]. Circulating Golgi protein 73, a gluconeogenic protein in the Golgi apparatus, is overexpressed in patients with COVID-19 infection, resulting in enhanced hepatic glucose output [12]. COVID-19 infection may activate interferon regulatory factor-1, which decreases insulin signaling through direct suppression of post-receptor action and increased cytokine production [17].

Increased levels of cytokines like interleukin (IL)-6, IL-1 beta (IL-1 β), and Tumor Necrosis Factor-alpha (TNF- α) are the hallmark of COVID-19 infection and contribute to insulin resistance and beta-cell dysfunction [18, 19]. TNF- α and IL-1 β impact insulin signaling at the post-receptor level by activating the Jun N-terminal kinase and inhibitor of nuclear factor kappa-B kinase subunit beta (IKK-beta), resulting in phosphorylation of insulin receptor substrate 1 (IRS-1) and upregulation of nuclear factor kappa B activity (through inhibition of its negative regulator (IkappaB kinase), respectively [20]. This reduces the action of insulin and positively reinforces the proinflammatory phase by increasing cytokine production. Levels of macrophage chemoattractant protein-1 are increased, which drives inflammatory cell infiltration (macrophages/T cells) in the adipose/muscle/liver tissue (major sites of glucose utilization) and causes decreased uptake of glucose [21].

Table 13.1 Key aspects of pathophysiology of COVID-19 and diabetes

| COVID-19-mediated effects | Outcomes |
|---|--|
| Activation of serine kinases | Altered adipokine secretion |
| ↑ myeloperoxidase production | ↑ insulin resistance |
| Overexpression of Golgi protein 73 | ↑ hepatic glucose output |
| Activation of interferon regulatory factor 1 | ↓ insulin signaling |
| ↑ TNF- α and IL-1 β | ↑ insulin resistance |
| ↑ macrophage chemoattractant protein-1 and ↑ inflammatory cell infiltration | ↓ glucose uptake |
| Infiltration of beta cells with SARS-CoV-2 [seen in mouse models] | ↓ glucose sensing, ↓ insulin production, accelerated apoptosis |
| The impact of glucocorticoids as part of COVID-19 treatment | |
| ↓ insulin action at post-receptor level | ↑ insulin resistance and ↓ decreased glucose uptake by cells |
| ↑ hepatic gluconeogenesis | ↑ hepatic glucose output |

Data from mouse models and humans have shown marked beta-cell dysfunction in patients with SARS-CoV-2 infection. Similar pathology has also been noted in previous SARS-CoV-2 pandemics [22]. Population analysis has pointed towards a potential increase in incidence of type 1 diabetes during the pandemic [23–25]. Cellular and autopsy studies in patients with COVID-19 disease have demonstrated infiltration of beta cells with SARS-CoV-2 and cellular changes consistent with suboptimal function [26, 27]. Beta-cell membranes express Neuropilin-1, angiotensin-converting enzyme 2, dipeptidyl peptidase 4, and transmembrane serine protease 2, which may promote COVID-19 cellular entry [27]. Viral entry and replication cause acute local inflammation and changes in the transcription patterns, leading to decreased glucose sensing, inadequate insulin production and accelerated cellular apoptosis of the beta-cell mass [27]. Trans-differentiation of infected pancreatic beta-cell models also reduces insulin production [28]. However, most data of beta-cell dysfunction is from ex vivo cellular models and data on the in vivo impact of COVID-19 infection on pathophysiologic factors for diabetes in humans is not robust.

Dexamethasone and remdesivir are the primary treatment strategies for COVID-19 infection in hospitalized patients. Dexamethasone has been shown to reduce inpatient mortality in patients requiring respiratory support but may result in new onset hyperglycemia in at-risk patients and exacerbate hyperglycemia in patients with diabetes [29]. The risk is dependent on dose and duration, body mass index, and age. Hyperglycemia is typically post-prandial. Glucocorticoids inhibit insulin action at a post-receptor level, resulting in increased insulin resistance and decreased tissue glucose uptake by skeletal muscle and adipose tissue with inhibition of glucose transporter type 4 expression [30, 31]. Glucocorticoids may result in increased glucose production from liver by stimulating rate-limiting enzymes (phosphoenolpyruvate carboxykinase) of hepatic gluconeogenesis and increasing concentration of gluconeogenic substrates (amino acids, glycerol produced through muscle/adipose tissue catabolism) [32]. Glucocorticoids impact beta-cell function directly by impacting beta-cell lifespan and secretory capacity [33–36]. Remdesivir did not result in increased hyperglycemia in phase 3 trials and impact on patients with diabetes in the general population is unknown [37, 38].

The end result of uncontrolled hyperglycemia and insulin resistance leads to increased rates of acute complications of hyperglycemia and worse COVID-19 outcomes [39]. Rates of DKA are increased in patients with COVID-19 [40], both with and without a diagnosis of diabetes, and the outcomes of DKA including hospital stay and morbidity/mortality are worse in the SARS-CoV-2 infected patients compared to non-infected patients [41–44].

Newly Diagnosed Diabetes in Patients with COVID-19

Newly diagnosed diabetes has been found to be common at the time of admission with COVID-19 infection. It remains unclear whether patients who were otherwise predisposed to diabetes merely received a “final push” with contraction of the COVID-19 virus, if the virus directly leads to defective beta-cell function or insulin resistance [45] or a combination of the two. Another possibility is that diabetes was already present but went undiagnosed related to lack of medical care and follow-up, particularly during the pandemic years.

Healthcare Disparities

One recent study found that COVID-19 patients with new onset diabetes tended to be younger, non-white and have Medicaid insurance as opposed to Medicare or private insurance [46]. This may represent a subset of the population that lacks routine access to healthcare and who did not otherwise know they had diabetes prior to presentation. These patients also tended to have higher levels of inflammatory markers at presentation and more frequent admission to the intensive care unit indicating a severe inflammatory response itself may be contributing to newly diagnosed diabetes. This study used a threshold of ≥ 300 mg/dl as a cut off for newly diagnosed diabetes to avoid categorizing those with stress-induced hyperglycemia. Even so, on follow-up 40.6% of patients regressed to normoglycemia or prediabetes. This is similar to a study from Italy that demonstrated 63% regression to normoglycemia in COVID-19 patients with newly diagnosed diabetes on follow-up [10]. The finding that many patients who are diagnosed with diabetes at the time of presentation to the hospital with COVID-19 later develop remission of diabetes supports the thought that stress-related insulin resistance, rather than direct beta-cell injury, may be the primary driver of hyperglycemia.

Case 1

A 59-year-old male patient presented to the emergency department with subjective fevers, shortness of breath, myalgias, and non-purulent productive cough for 3 days. The patient attended a wedding party 4 days before symptoms onset. Past medical history included type 2 diabetes, hypertension, tobacco use disorder, and osteoarthritis. Patient was on metformin 1000 mg twice daily, sitagliptin 100 mg daily, amlodipine 5 mg daily, and acetaminophen as needed at home. On presentation, temperature was 101 °F, pulse 116 beats per minute, blood pressure 140/95 mmHg, respiratory rate 32 breaths per minute, and oxygen saturation 82% on room air. Laboratory evaluation on presentation was notable for mild hyperglycemia (190 mg/dL) and acute

kidney injury (creatinine 1.7 mg/dL, baseline 0.8 mg/dL). COVID-19 PCR resulted positive. X-ray imaging noted bilateral multi-lober opacities. The patient was started on supplemental oxygen therapy with nasal cannula at 4 L/min. Oxygen saturation improved to 91%. Patient was admitted for severe COVID-19 infection and treatment was initiated with remdesivir and dexamethasone 6 mg/daily. Patient's blood glucose worsened just a day after dexamethasone was initiated (Fig. 13.1). Home anti-hyperglycemic medications were held, and the patient was initiated on low-dose correctional scale insulin aspart, with suboptimal control. The patient was requiring 20–30 units of insulin aspart/day for the next 2 days. Insulin regimen was changed to basal-bolus regimen, with 10 units of insulin glargine once daily and 7 units of insulin aspart with meals (30% basal/70% bolus) plus correctional scale aspart. Blood glucose values showed significant improvement, with further titration of insulin to 10 units of insulin aspart with meals and 12 units of insulin glargine once daily.

Discussion

Treatment with supraphysiologic, dexamethasone 6 mg/day for 10 days is recommended for patients admitted with COVID-19 pneumonia requiring supplemental oxygen. Glucocorticoid-mediated hyperglycemia is a common side effect of high-dose glucocorticoid therapy in hospitalized patients [47, 48]. Persistent hyperglycemia is associated with increased duration of hospital stay, infectious complications, and inpatient mortality [49–51]. Treatment strategies in steroid-induced hyperglycemia depend on steroid formulation, dose and duration of glucocorticoid use [52]. Treatment guidelines for steroid-induced hyperglycemia and recommendations are

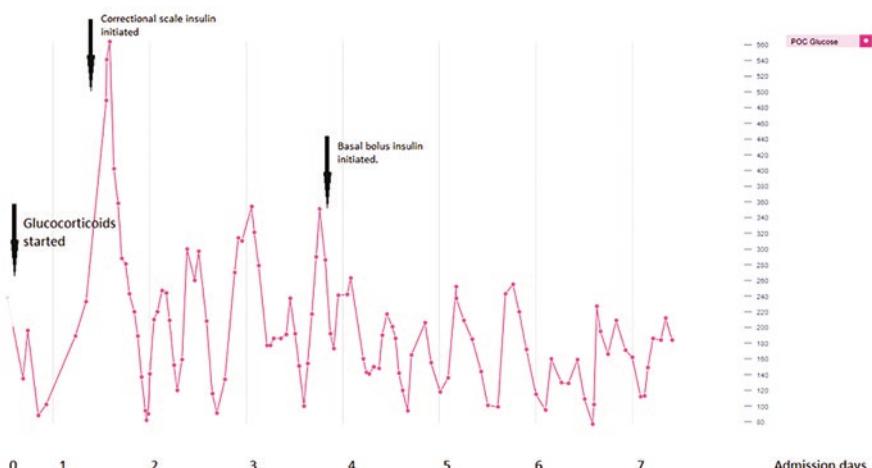


Fig. 13.1 Glycemic variation of patient during hospitalization: Glucose levels increased significantly the day after initiation of dexamethasone, and improved on initiation of basal-bolus regimen

based on small-scale studies and institutional experience [53–57]. Treatment of inpatient steroid-induced hyperglycemia should be strongly considered if ≥ 2 blood glucose readings are ≥ 180 mg/dL.

Insulin is the treatment of choice, given its immediate action and titratable nature. Mild hyperglycemia is initially treated with medium- to high-dose correctional scale short-acting insulin. If daily requirements exceed 10 units/day or if the patient has persistent hyperglycemia, a transition to scheduled dosing is recommended, with an initial starting dose of 0.3–0.6 units/kg/day for an insulin naïve patient. Patients who are already on insulin should have their total daily dose increased to at least 0.4–0.6 units/kg/day [58]. Basal-bolus regimen is the most commonly used scheduled regimen, with a higher proportion of nutritional short-acting insulin to meet the post-prandial requirements: 60–70% of daily dosing should be bolus insulin.

Use of NPH insulin is another appropriate strategy [59]. Pharmacokinetics of NPH insulin closely match the hyperglycemic trend of intermediate acting glucocorticoids (prednisone), with action of morning NPH dose peaking around lunch and having no activity overnight, thus reducing the risk of hypoglycemia. Studies have shown equal efficacy compared to long-acting insulin analogs (insulin glargine, insulin degludec) [55, 56]. Total daily NPH dosing can be divided to 70% with breakfast and 30% with dinner in patients with dexamethasone use, or daily timed with dexamethasone administration. In critically ill, intubated patients with COVID-19 pneumonia and severe hyperglycemia, an insulin infusion should be considered for management.

Insulin requirements can change dramatically and daily titration is typically required, particularly in the early stages and with changing glucocorticoid doses with target blood glucose of 140–180 mg/dL [60]. Hyperglycemia does not immediately reverse after glucocorticoids are stopped, requiring 2–4 days depending on formulation and dose reduction should be followed closely. Follow-up is important to evaluate risk of persistent hyperglycemia in patients who had preexisting risk of diabetes and in view of possible increased risk of diabetes post-COVID-19 infection.

Oral agents are not recommended, unless the patient strictly wants to avoid insulin, is clinically stable and has mild hyperglycemia with a long duration of glucocorticoid use planned. Oral agents are slow in action, taking a few days to act and might not target the post-prandial hyperglycemia as well. Inpatient use can be limited due to contraindications. DPP-4 inhibitors may be used in hospitalized patients with type 2 diabetes, mild hyperglycemia, and non-critical illness in the inpatient setting [60].

Case 2

A 39-year-old female with no significant past medical history presented to the hospital for worsening shortness of breath and cough for 3 days. She also noted loss of taste, dry mouth, and increased thirst for 1 week. She was found to be tachypneic

with a respiratory rate of 26 and hypoxic with SaO_2 of 86% on the initial exam. Her SARS-CoV-2 polymerase chain reaction was positive. Her vitals stabilized following nasal cannula oxygen supplementation. Laboratory data was notable for a random blood glucose of 389 mg/dL. Subsequent HbA1c was found to be elevated to 10.3% (5.4% two years prior). She was admitted to a dedicated COVID-19 inpatient medical unit and started on insulin glargine 10 units at bedtime, low-dose insulin aspart correctional scale before meals and point-of-care glucose monitoring using fingerstick. As she was insulin naïve, low doses of basal insulin were selected initially (approximately 0.1 unit/kg body weight). Shortly after admission, she was transitioned to a continuous glucometer in lieu of point-of-care fingerstick to allow close monitoring of the patient's hyperglycemia.

She was noted to have marked hyperglycemia following initiation of dexamethasone 6 mg/daily and insulin regimen is adjusted accordingly to target premeal blood glucose of 140–180 mg/dL. She ultimately required insulin glargine 24 units at bedtime with nutritional insulin aspart 16 units with meals and a high-dose correctional scale with meals. The ratio of 30% basal and 70% nutritional insulin was selected to account for significant post-prandial hyperglycemia associated with glucocorticoid therapy.

As her HbA1c was markedly elevated prior to initiation of steroids, once her oxygen requirement have improved and her steroid course has finished, the decision is made to discharge her on a basal-bolus insulin regimen of insulin glargine 24 units at bedtime and insulin aspart 8 units with meals, approximately 0.5 units/kg/day as her total daily dose, split between basal and nutritional insulin in a ratio of 50:50 reflecting a more balanced basal and nutritional regimen.

At her first outpatient follow-up visit 6 weeks later, she reported that she is no longer taking the mealtime insulin as she was experiencing frequent low blood glucose. She continued the basal insulin but noted that she will have low blood glucose overnight or in the early morning hours if she did not have a bedtime snack heavy in carbohydrates such as cookies. She was overwhelmed with her new diagnosis of diabetes and asked if she will require insulin for the rest of her life.

Anti-glutamic acid decarboxylase antibody titers were negative and C-peptide was 2.0 ng/mL (reference range 0.8–3.85 ng/mL). Her basal insulin was reduced by 50%, and she was started on metformin 500 mg twice daily. She was recommended to only check fasting blood glucose and if she is symptomatic. At her next follow-up, she can discontinue insulin after review of her fasting blood glucose, up titration of her metformin and addition of a GLP-1 agonist, Dulaglutide.

Discussion

Patients who are newly diagnosed with type 2 diabetes during hospitalization for COVID may have been those that are not routinely followed by outpatient providers and living with chronic hyperglycemia for months and even years prior to infection. Hospitalization may be a unique opportunity to diagnose diabetes that may have otherwise not been diagnosed. These patients tended to be from under-insured and

historically marginalized communities including blacks and Latinos. We therefore favor the term “Newly diagnosed diabetes” as opposed to “new onset diabetes.” Indeed, the Centers for Disease Control and Prevention made changes in the COVID-19 reporting system to include data on race and ethnicity in June 2020 after hundreds of healthcare professionals and civil rights groups urged the U.S. government to release this data to reveal the true impact of the virus on communities of color.

COVID-19 infection acutely led to stress hyperglycemia that in the days and weeks prior to hospitalization could lead to worsening glycemic control in patients who are otherwise predisposed to hyperglycemia (e.g., patients with prediabetes). Many patients present with symptoms of severe hyperglycemia such as increased thirst and urination, weight loss in addition to symptoms of acute viral infection, i.e., fever, cough, and shortness of breath.

Several patients have also been diagnosed with new onset type 1 diabetes following onset of COVID-19 infection. Early during the pandemic, there were anecdotal reports of new onset type 1 diabetes raising concerns that the virus may itself drive destruction of beta cells, however, subsequent population-based studies failed to find a strong link [61]. Patients presenting with new onset diabetes who otherwise do not have clinical or physical evidence of insulin resistance should be checked for antibodies associated with type 1 diabetes such as Glutamic Acid Decarboxylase-65 antibodies. C-peptide may be falsely low in the setting of severe hyperglycemia and glucotoxicity state which can suppress endogenous insulin secretion transiently. Recommendation should be for close outpatient follow-up and C peptide measurement after the acute hyperglycemic state has resolved, perhaps 6–8 weeks later.

The components of stress hyperglycemia and steroid-induced hyperglycemia during acute illness can quickly resolve during recovery, and patients should be given instructions on how to de-escalate therapy or mitigate hypoglycemia at time of discharge from the hospital [58]. Close follow-up is necessary for all patients, in particular those newly diagnosed with diabetes who require extensive education on diabetes self-management that may not be possible in the hospital setting.

The COVID-19 pandemic forced development of more innovative healthcare solutions including research into the use of CGM in critically and non-critically ill patients in the hospital, largely showing comparable efficacy to POC measurements in most patients, good uptake by nursing staff and potentially improved glycemic control and reduced rates of hypoglycemia.

Continuous Glucose Monitoring Use in the COVID-19 Pandemic

Currently, the American Diabetes Association Standards of care recommends point-of-care (POC) glucose as the recommended method of glucose monitoring in the hospital [60, 62]. Though continuous glucose monitoring (CGM) systems have

been approved for outpatient use by the U.S. Food and Drug Administration since 1999, studies on its inpatient use had been limited to non-critically ill patients. The onset of the COVID-19 pandemic led to unprecedented strains on our existing healthcare infrastructure, overwhelmed with patients who required strict isolation and close glucose monitoring, many of whom either had preexisting or a new diagnosis of diabetes. In April 2020, the U.S. Food and Drug Administration announced it would not object to the provision of CGM systems for the treatment of patients in hospital settings to support COVID-19 healthcare-related efforts during the pandemic [63].

Use of CGM in the critical care setting posed several concerns including its accuracy in the setting of sensor compression due to patient positioning, changes in tissue perfusion, acid base balance and edema. More practical concerns about training of already overworked nursing staff to use CGM were also raised. The multidisciplinary team at Ohio State University Hospital was among the first to publish the results of their hybrid POC-CGM model for patients requiring intravenous insulin [64, 65]. They showed not only safety and acceptance by nursing staff of such a protocol but also its potential for conserving personal protective equipment, improving hospital efficiencies, and improving glycemic control. Since then, multiple hospital organizations have published their data on the safety and accuracy of CGM use in the hospital setting [66] that could pave the way for more widespread inpatient use of this technology in the future.

Multidisciplinary Approach to Patients with COVID-19 and Diabetes

COVID-19 has placed unprecedented strains on the healthcare system, highlighting the inequities in healthcare for patients of minority populations and of lower socio-economic groups. Nevertheless, in meeting the challenges of the pandemic, hospital systems have developed new and innovative approaches for caring for patients with COVID-19 effectively. These changes included elevating the role of inpatient diabetes providers and evolution of multidisciplinary teams including endocrine hospitalists, nurse practitioners, physician assistants, nurses, and diabetes education specialists that are tasked with caring for patients with diabetes using a centralized approach [67]. This not only allows for more deliberate, efficient, and guideline-based adjustment in diabetes regimens but allows patients to have access to diabetes professionals as part of their care team who can guide them through each step of their glycemic management [68–70]. Some new strategies that are in development include use of telemedicine for inpatient diabetes management and inpatient use of CGM in both critical and non-critical care settings [71]. Many hospital systems have already implemented telemedicine as a means of overcoming staffing shortages and allow access to diabetes specialists in smaller hospitals that would otherwise not have access to such providers.

Conclusion

COVID-19 and diabetes mellitus have a bidirectional relationship, and it is vital to consider the impact of one on the other when managing patients in the inpatient setting.

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Chapter 14

Overview of Inpatient Management of Hypertriglyceridemia Associated Acute Pancreatitis in Patients with Diabetes Mellitus



Fuad Benyaminov and Avani Sinha

Introduction

Both Type 1 diabetes mellitus (T1DM) and Type 2 diabetes mellitus (T2DM) are associated with pancreatitis and increased inflammation. The mechanism for this increased inflammation is different in T1DM than in T2DM. In T1DM, the predominant theory is that CD4+ and CD8+ T cells (effector T cells/Teff) target several beta cell autoantigens and related peptide epitopes causing beta cell pancreatic islets inflammation, called insulitis [1]. The three cytokines that appear to be involved in the inflammation of pancreatic beta cells in T1DM are the synergic action of interferon gamma (IFN-gamma) and inflammatory cytokines TNF-alpha and IL-1beta [2]. The combined action of these inflammatory molecules results in the upregulation of inducible nitric oxide synthase with subsequent production of nitric oxide [3].

T2DM is often linked with obesity and metabolic syndrome, which is positively associated with concentrations of inflammatory biomarkers [4–6]. White adipose tissue (WAT) and mainly visceral WAT seems to be the major source of

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inflammatory markers in T2DM [7]. It produces cytokines and several other bioactive substances involved in the inflammatory pathways, such as TNF-alpha, IL-1, IL-6, IL-10, leptin, adiponectin, monocyte chemoattractant protein, angiotensinogen, resistin, chemokines, serum amyloid protein, and many others collectively referred to as adipokines [7–10]. Further infiltration of adipose tissue by macrophages and immune cells (B cells and T cells) trigger local and systemic chronic low-grade inflammation, by producing more cytokines and chemokines that serve as a pathologic link between obesity, insulin resistance, and diabetes mellitus (DM) [11]. Macrophages also seem to play a key role in pancreatic islet inflammation, with one study finding an increased number of islet-associated macrophages in T2DM [12].

Pancreatitis is an inflammatory disorder of the pancreas which is associated with increased risk of pancreatic cancer and premature mortality [13]. High alcohol intake, smoking, obesity, elevated triglyceride levels, and a history of gallstones are among the established or suspected risk factors for pancreatitis [13]. Aune et al. performed a meta-analysis on the associated risk between DM and acute pancreatitis, which included 8 prospective cohort studies and found that in patients with DM, the relative risk of developing acute pancreatitis was 1.74 (95% CI: 1.33–2.29) when compared with patients without DM [14]. Another cohort study found similar results, with a hazard ratio (HR) of 1.49 (95% CI: 1.31–1.70) even after controlling for common comorbidities such as age, gender, obesity, smoking, alcohol use, or gallbladder disease [15].

Hypertriglyceridemia and Acute Pancreatitis

Hypertriglyceridemia is the third most common cause of acute pancreatitis (AP), accounting for approximately 10% of cases, after gallstones and alcohol [16]. AP is associated with significant mortality with a fatality rate of about 5% and places a substantial burden on the healthcare system in the USA, as it accounts for approximately 275,000 hospitalizations annually with a total attributable healthcare cost of \$2.6 billion/year [17–19]. Although most AP patients have a mild disease course with focal interstitial inflammation of the pancreas, about 20% of patients develop systemic inflammatory response syndrome (SIRS) and subsequent organ dysfunction [20]. This group of AP patients typically requires intensive care unit (ICU) management, prolonged hospitalization, and an associated mortality rate as high as 30% [20]. The exact mechanism of hypertriglyceridemia-induced pancreatitis (HTGP) is not clearly understood, but the most accepted mechanism suggests hydrolysis of triglycerides by pancreatic lipase, in and around the pancreas, leading to the production of free fatty acids in pancreatic capillaries [21, 22]. These fatty acids accumulate in capillaries leading to pancreatic ischemia with acidosis, trypsinogen activation, and the initiation of AP [21, 22]. Hyper-viscosity from excessive triglycerides in pancreatic capillaries leading to ischemia has also been proposed [23]. Hypertriglyceridemia is present in more than half of patients with diabetes

mellitus [24]. Patients with T2DM and insulin resistance tend to have hypertriglyceridemia due to increased hepatic VLDL production as well as delayed clearance of triglycerides [25]. There may also be an increased flux of free fatty acids (FFAs) from adipose tissue to the blood stream because of insulin resistance indirectly leading to the activation of lipoprotein lipase (LPL) in adipose tissue [21, 26].

Management of Acute Pancreatitis Secondary to Hypertriglyceridemia

The initial management of HTGP is similar to that applied to treat acute pancreatitis of other causes, which includes bowel rest, aggressive IV hydration and symptomatic care including pain management [27]. Following the initial management of HTGP, it is imperative to next aim to lower serum triglyceride to decrease the risk of relapse. Furthermore, maintaining triglyceride levels below 500 mg/dL has been shown to expedite clinical improvement [27].

Insulin therapy has been the first-line agent in treating hypertriglyceridemia-induced pancreatitis due to its ability to rapidly lower triglyceride levels by activating the enzyme LPL which causes chylomicron degradation thus lowering triglyceride levels [28]. Insulin is also effective in treating acute pancreatitis because it causes the pancreatic tissue to relax and may improve immunoparalysis via upregulating the expression of human leukocyte antigen on monocytes and decreasing cell apoptosis [29]. Insulin can be administered subcutaneously or intravenously as a continuous infusion. It has been reported that the IV route of administration is more convenient in contrast to the subcutaneous route of administration as it is easier to titrate the dose of insulin based on the pharmacokinetic parameters [30]. In addition, treatment with IV insulin was found to lower serum triglyceride levels by 40% in 24 h, compared to 23% with the subcutaneous route [30].

The optimal dose rate of insulin and dextrose infusions has been a point of contention for providers caring for patients with HTGP. Several different doses of insulin, including intermittent and continuous infusions, have been proposed from the data of case reports and case series. The most consistent efficacy is reported with an insulin infusion at 0.1 unit/kg per hour with a simultaneous dextrose 5% infusion to avoid hypoglycemia [31–35]. To the contrary, Badiu et al. suggested that even low-dose insulin (1–2 units per hour) is usually efficient to block adipose tissue lipolysis, reduce circulating free fatty acids levels, and theoretically reduce triglyceride production by the liver [36]. Badiu et al. writes that higher doses of insulin, such as those used to treat diabetic ketoacidosis, require large amounts of glucose infusion to prevent hypoglycemia and are likely to increase de novo triglyceride production in the liver [36]. Triglyceride levels usually fall by 50% in the first 24 h, with most cases reaching levels of less than 500 mg/dL in 3–4 days [36, 37]. Insulin is typically given as a continuous infusion and is continued until triglycerides are <500 mg/dL [38]. For patients receiving insulin infusion therapy, the American

Diabetes Association and American Association of Clinical Endocrinologists recommend hourly blood glucose monitoring except for patients with stable blood glucose within the target range, for whom monitoring can be performed every 2 h [39, 40, 81]. According to the current recommendation of the American Diabetes Association, a target blood glucose concentration of 140–180 mg/dL is recommended for the majority of critically ill and noncritically ill patients to reduce the risk of hypoglycemia [40]. Failure of insulin infusion can be considered when patients are developing worsening organ dysfunction while on insulin infusion or if insulin infusion fails to decrease triglyceride levels adequately [38].

Plasmapheresis is another therapeutic modality for HTGP if insulin treatment fails or if the patient's condition worsens. The American Society of Apheresis guidelines have approved the use of therapeutic plasmapheresis in severe HTGP, in the setting of worsening organ dysfunction or multi-organ failure, worsening systemic inflammation, or lactic acidosis [41]. Plasmapheresis removes triglycerides and chylomicrons from the circulation. The justification for the use of plasmapheresis is to significantly decrease triglyceride levels and reduce inflammatory cytokines [41]. A single session of plasmapheresis has been reported to lower triglyceride levels by 50–80% [23]. Although multiple case series report the benefit of plasmapheresis in management of HTGP, the only prospective study to date with a control group (60 versus 34 patients) did not show any mortality benefit compared to conservative management [42]. Delay in initiating plasmapheresis was believed to be a possible reason for this lack of difference in mortality [42]. Another large retrospective study including 111 patients treated with plasmapheresis also found no mortality benefit in patients who received early plasmapheresis (within 36 h) versus late plasmapheresis (>36 h) for HTGP [43]. Plasmapheresis is not without adverse risks. It requires central venous access, can be expensive, has the possibility for infections or allergic reactions, and may have limited availability. Plasmapheresis is an encouraging area of research as it successfully decreases serum triglyceride levels in HTGP; however, more randomized controlled trials (RCTs) are needed to sufficiently evaluate the benefits and risks of this therapeutic option.

After the acute management of HTGP, it is essential to focus on the future suppression of triglyceride levels in order to prevent recurrent disease. This is accomplished with lifestyle modifications and pharmacological therapies. The ideal target triglyceride level is not well-defined; however, levels <500 mg/dL are generally an acceptable goal [44]. Newer studies including retrospective cohort studies have found the lowest rates of recurrence of acute pancreatitis when the follow-up serum triglyceride levels are lower than 200 mg/dL, suggesting a lower target triglyceride level should be achieved to prevent recurrent disease [45, 46]. Implementation of lifestyle modifications include exercise, weight loss, limiting intake of simple sugars and dietary fat (<15% of energy), alcohol and smoking cessation, as well as control of secondary risk factors such as DM and minimizing the use of medications that can elevate triglyceride levels [36, 47]. A registered dietitian should be consulted while the patient is in the hospital to discuss these dietary modifications further. Common medications that are known to increase triglyceride levels include thiazide diuretics, non-selective beta blockers, estrogenic compounds (such as oral

contraceptives), corticosteroids, protease inhibitors, immunosuppressives, antipsychotics, antidepressants, and retinoids [48]. Minimizing the use of these medications can help prevent hypertriglyceridemia. For patients with secondary risk factors for hypertriglyceridemia, such as uncontrolled DM, discharging the patient on insulin should be considered as this may be optimal in assisting with both hyperglycemia and hypertriglyceridemia.

Pharmacologic treatments include lipid-lowering medications such as fibrates, statins, and omega-3 fatty acids. See Table 14.1 for a summary of medications and mechanisms of actions to decrease triglyceride levels. The decision on which pharmaceutical agent to choose from depends on triglyceride levels. In cases with triglyceride levels >500 mg/dL, the primary goal would be the reduction of triglyceride level to less than 500 mg/dL to prevent the recurrence of acute pancreatitis hence fibrates are typically chosen due to their strong TG lowering efficacy as reviewed later [49]. However, in cases of mild-to-moderate triglyceride levels 150–500 mg/dL, we simultaneously focus on decreasing risk of recurrence of AP as well as risk of atherosclerotic cardiovascular disease (ASCVD); hence, statins are typically chosen as first-line therapy [50]. Subgroup analyses of trials such as 4S (Scandinavian Simvastatin Survival Study) and PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22) establish that statins reduce ASCVD risk in patients with elevated triglyceride levels [51, 52]. Although primarily effective for lowering LDL-C levels, statins can lower triglyceride by 10–30% [53]. Statins demonstrate this triglyceride reducing effect by enhancing VLDL clearance and decreasing lipoprotein production [36].

Fibrates are primarily used to treat hypertriglyceridemia when triglyceride levels are above >500 mg/dL due to its strong effect on decreasing serum triglycerides by 30–50% [53]. Fibrates activate peroxisome proliferator-activated receptors (PPAR) α , which promotes fatty acid oxidation, increasing LPL activity and results in a decrease of triglyceride levels and an increase in HDL levels [36]. The main side effects of fibrates are myopathy, cholelithiasis, and liver enzyme elevation [23]. Fenofibrate may be taken once daily while gemfibrozil is given twice a day with

Table 14.1 Summary of hypertriglyceridemia interventions and their mechanisms

| Class of medication/interventions | Mechanism of action of decreasing triglyceride levels |
|-----------------------------------|--|
| Insulin | Activates the enzyme LPL which causes chylomicron degradation thus lowering triglyceride levels |
| Plasmapheresis | Removes triglycerides and chylomicrons from the circulation |
| Fibrates | Activates peroxisome proliferator-activated receptors (PPAR) α , which promotes fatty acid oxidation Increases LPL activity and resulting in a decrease of triglyceride levels |
| Statins | Inhibits HMG-CoA reductase, decreasing VLDL secretion Enhances VLDL clearance and decreases lipoprotein production |
| Omega-3 fatty acids | Decreases hepatic secretion of VLDL |
| Niacin | Decreases VLDL secretion via an unclear mechanism |

meals but is used less often due to a less favorable drug interaction profile, as described below. Fenofibrate is renally excreted, and the dosage should be adjusted in patients with kidney disease. The National Kidney Foundation recommends fenofibrate dose decrease by 50% if the glomerular filtration rate (GFR) is 60–90 mL/min/1.73 m², decrease by 75% if the GFR is 15–59 mL/min/1.73 m², and to avoid fenofibrate in patients on dialysis or with a GFR <15 mL/min/1.73 m² [54]. The National Kidney Foundation states that dose modification for decreased kidney function is not required for gemfibrozil [54]. Conversely, the National Lipid Association Safety Task Force recommends that gemfibrozil dose be reduced by 50% if the GFR is 15–59 mL/min/1.73 m² and to avoid gemfibrozil for GFR <15 mL/min/1.73 m² [55].

In hypertriglyceridemia, fibrates may be used synergistically with statins and the combination should be considered in patients with HTG that is insufficiently managed with monotherapy alone [23]. The combination of gemfibrozil and most statins is associated with an elevated risk of myopathy due to increased statin blood levels, while fenofibrate is not involved with statin metabolism and is preferred in fibrate/statin combination regimen [55].

Omega-3 fatty acids, which include eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are thought to decrease serum triglyceride levels by decreasing hepatic secretion of VLDL [56, 57]. Omega-3 fatty acids are indicated for triglycerides higher than 500 mg/dL and decrease triglyceride levels by 20%–50% depending on the baseline levels [53]. In contrast to fibrate medications, omega-3 fatty acids do not interfere with statin metabolism and do not cause myopathy as a side effect [53]. The REDUCE-IT study (Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial) was an RCT comparing statin use to a combination of statin with a high dose (4 g daily) of a specific omega-3 fatty acid (icosapent ethyl = EPA ethyl ester) in patients with hypertriglyceridemia. The trial found that the incidence of cardiovascular events was greatly reduced (hazard ratio, 0.75; 95% confidence interval [CI], 0.68–0.83; $P < 0.001$) [58]. Of note in the same study, a larger percentage of patients in the icosapent ethyl group than in the placebo group were hospitalized for atrial fibrillation or flutter (3.1% vs. 2.1%, $P = 0.004$) [58]. It is important to bring attention to the controversy surrounding the interpretation of this trial since mineral oil was used as the placebo in the control group. Saturated, monounsaturated, and omega-6 polyunsaturated fatty acids found in various ratios in certain oils may impact various cardiovascular (CV) risk parameters differentially, including blood lipids, glucose metabolism, blood pressure, and inflammatory pathways. Kastelein et al. suggested that the observed reduction in CV risk of REDUCE-IT study might be attributable to the theoretical negative effects of mineral oil control rather than being due to the clinical benefits of icosapent ethyl, a claim based on elevations in some lipid levels and inflammatory markers in the placebo arm of the REDUCE-IT trial. Since this controversy, a review study was published analyzing 80 studies in which mineral oil was used as a placebo and concluded that mineral oil does not appear to change levels of lipids or impact medication absorption or efficacy, or related clinical outcomes, and, therefore, does not meaningfully affect study conclusions when used as a placebo at the quantities used

in clinical trials. Another observational study sought to compare differences in progression of total plaque and total non-calcified plaque volumes on coronary computed tomography angiography (CTA) in mineral oil placebo patients from EVAPORATE vs. the non-mineral oil placebo arm from another RCT. They concluded that progression of total plaque and total non-calcified plaque volumes on coronary CTA is not related to consumption of mineral oil in the quantities used in these placebo capsules and thus the results of REDUCE-IT, as well as several other trials using mineral oil placebo capsules, should not be affected by the choice of this placebo.

There are over-the-counter and prescription formulations of omega-3 fatty acids that have differing quantities of EPA and DHA, with prescription formulations usually containing double the amount of omega-3 fatty acids. Prescription formulations include brands such as Lovaza and Vascepa. Lovaza is made up of 0.465 g EPA and 0.375 g DHA in each 1-g capsule while Vascepa is made up of entirely of high-purity formulation containing icosapent ethyl, the ethyl ester of EPA, which was the formulation used in REDUCE-IT. In patients with triglyceride levels >500 mg/dL, studies have shown that Lovaza 4 g/day significantly reduced mean triglyceride concentrations by 45% ($P < 0.00001$), while Vascepa 4 g/day reduced the placebo-corrected triglyceride levels by 33.1% ($p < 0.0001$). The American Heart Association recommends 2–4 g/day of EPA plus DHA to decrease triglyceride levels.

Niacin, also known as vitamin B3, lowers plasma cholesterol and triglyceride levels by decreasing VLDL secretion via an unclear mechanism [36]. Although high-dose niacin therapy is useful in decreasing triglyceride levels by 20–50%, it is used much less frequently due to its common side effects which include flushing (30% of patients), pruritus, gastrointestinal disorders, hyperglycemia, blurring of vision, myopathy, worsening diabetes mellitus, and elevation of liver enzymes [53, 59]. Additionally, statin plus niacin combination therapy has not been shown to provide additional cardiovascular benefit above statin therapy alone and is generally not recommended due to the side effect profile mentioned above [60, 61]. Of note, cutaneous reactions to niacin, such as flushing and pruritus, can be significantly decreased with pre-treatment of 325 mg of aspirin [62].

Based on literature review, the suggested treatment protocol for a patient admitted for HTGP includes supportive care, admission to the intensive care unit and initiation of intravenous insulin and dextrose infusions with close monitoring. Glucose levels should be checked hourly while on intravenous insulin infusion and triglyceride levels can be checked daily or twice a day. When the triglyceride levels fall lower than 500 mg/dL, intravenous insulin infusion can be transitioned to either a subcutaneous insulin regimen or discontinued completely depending on hemoglobin A1c levels. Failure to respond to closely titrated insulin infusion within 24–48 h or clinical worsening should prompt consideration of plasmapheresis. If the patient is tolerating an oral diet, oral anti-hypertriglyceridemic agents should be started (statin, fenofibrate, omega-3 fatty acids). When oral diet is resumed, it should consist of a low-fat diet (<15% of energy) with avoidance of simple sugars and a registered dietitian should assist the patient with counseling of dietary modifications.

[47]. Triglyceride levels should be monitored after re-introducing oral diet to ensure levels do not increase significantly.

For patients with severely uncontrolled DM on admission, discharging with a subcutaneous insulin regimen will likely be optimal as it will assist with suppressing both glucose and triglyceride levels. For patients being started on insulin for the first time, proper insulin training should be performed with appropriate technique observed prior to discharge. Patients with milder elevation of HbA1c may not require insulin on discharge but should receive appropriate pharmacotherapy (e.g., metformin). Some classes of DM medications with a possible risk of pancreatitis may be avoided at the time of discharge (see discussion below). In addition, providers should confirm that diabetes medications and supplies are covered by insurance and affordable for the patients to obtain. Close follow-up should be established with an endocrinologist to ensure triglyceride and glucose levels are within target range.

Discussion of Diabetes Drugs and Risk for Pancreatitis

While DM is associated with increased inflammation and pancreatitis, certain diabetes therapeutics have also been proposed to be linked to an increased risk of acute pancreatitis. When glucagon-like peptide-1 receptor agonists (GLP-1RA) were first introduced, the medication was observed to have an increased risk of acute pancreatitis [63]. Given the limitations of observational studies, the results may have been confounded since patients with diabetes mellitus may also have accompanying comorbidities that may increase the risk for acute pancreatitis. Longer term RCTs were subsequently performed to add more data to this discussion. In the Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN) 6 trial, acute pancreatitis occurred in 9 semaglutide-treated patients, and in 12 placebo-treated patients. Pancreatic cancer occurred in one and four patients, respectively [64]. In the Peptide Innovation for Early Diabetes Treatment (PIONEER) 6 trial, AP occurred in one semaglutide-treated patient, and in three placebo-treated patients [65]. The incidence of pancreatic cancer was not reported. When combining all phase 3a data, pancreatitis occurred in five semaglutide-treated patients in PIONEER (six in the comparator group), and in 15 patients in SUSTAIN (13 in the comparator group). However, it is possible that since pancreatic cancer is a relatively rare complication, the RCTs and phase 3 studies had inadequate power to show differences between groups. When combining all available RCTs (including those from non-semaglutide GLP-1RAs) in a meta-analysis, a hazard ratio of 1.05 (95% confidence interval [CI] 0.78–1.40) was found for pancreatitis and 1.12 (95% CI 0.77–1.63) for pancreatic cancer [66]. These results consequently contradict the initial observational studies, arguing against an effect of GLP-1RA on pancreatitis and pancreatic cancer incidence. It is important to recognize that the follow-up duration in the RCTs (ranging from a median of 1.3–5.4 years) may not have been long enough for patients to develop pancreatic cancer [67].

While the RCTs argued against an effect of GLP-1RA on pancreatitis and pancreatic cancer incidence, other studies found an asymptomatic increase in plasma lipase and amylase levels [68, 69]. In a 26-week RCT, oral semaglutide dose-dependently increased lipase levels by 9–55% and subcutaneous semaglutide by 36% [70]. An increase in enzyme levels was not associated with occurrence of pancreatic events in trials with liraglutide in humans [71, 72]. In addition, it was previously demonstrated that the liraglutide-induced increase in pancreatic enzymes is not associated with changes in pancreatic exocrine function or pancreatic size measured by magnetic resonance imaging [73]. Similar research has not yet been performed for semaglutide. Even though pancreatic adverse events are hard to definitely exclude, an evaluation by the Food and Drug Administration and the European Medicines Agency concluded that a causal association between GLP-1RA and pancreatitis or pancreatic cancer is unable to be made with the present literature [74]. The current recommendations for patients on GLP-1RA are to monitor for symptoms of pancreatitis and in case of suspected pancreatitis, GLP-1 RAs are to be discontinued and should not be restarted if pancreatitis is confirmed [75].

Dipeptidyl Peptidase-4 (DPP-4) Inhibitors increase endogenous levels of glucagon-like peptide-1 (GLP-1) by inhibiting the DPP-4 enzyme which converts GLP-1 into its inactive form [76]. DPP-4 inhibitors have been also suggested to increase the risk of acute pancreatitis; however, the data has not been consistent (see Table 14.2 for list of DPP4 and GLP-1RA). Zhang et al. suggested that DPP-4 inhibitors were not associated with the increased risk of pancreatitis, while another recent meta-analysis of three RCTs showed a statistically significant increase in incidence of acute pancreatitis when compared with the control groups (odds ratio 1.79 [95% CI 1.13–2.82], $P = 0.013$) with an absolute risk reduction of 0.13% [77, 78]. Earlier meta-analyses of observational studies did not show an association between DPP-4 inhibitor use and AP [79, 80]. Similar to GLP-1RA, the current recommendations for patients on DPP-4 inhibitors are to monitor for symptoms of pancreatitis and in case of suspected pancreatitis, DPP-4 inhibitors are to be discontinued and should not be restarted if pancreatitis is confirmed [75]. In addition, the American Association of Clinical Endocrinology (AACE) recommends to consider alternative antihyperglycemic therapies to GLP-1RA and DPP-4 inhibitors in persons with a history of pancreatitis [81]. Contrary to this recommendation by AACE,

Table 14.2 List of GLP-1RA (left) and DPP-4 inhibitors (right)

| GLP-1RA | DPP-4 inhibitors |
|--|--------------------------|
| Exenatide (SQ, twice a day) | Sitagliptin (oral daily) |
| Liraglutide (SQ, daily) | Saxagliptin (oral daily) |
| Lixisenatide (SQ, daily) | Linagliptin (oral daily) |
| Exenatide long-acting (SQ, weekly) | Alogliptin (oral daily) |
| Dulaglutide (SQ, weekly) | |
| Semaglutide (SQ, weekly or oral daily) | |
| Tirzepatide (GLP-1RA + GIP combination) (SQ, weekly) | |

one retrospective study ($n = 161$) observed that in patients with a history of pancreatitis, those exposed to GLP-1RA had a similar rate of recurrent acute pancreatitis compared to the overall rate of recurrent AP [82]. Given that this is a small study, more studies are needed to investigate whether GLP-1RA and DPP-4 inhibitors can be used in patients with a history of pancreatitis.

Conclusion

Diabetes mellitus with associated comorbidities and pro-inflammatory state is a risk factor for developing acute pancreatitis. Patients with T2DM and insulin resistance may also have hypertriglyceridemia, which is a well-established cause of acute pancreatitis. Intravenous insulin infusion with intravenous dextrose is the mainstay treatment for hypertriglyceridemia-induced pancreatitis via rapid lowering of triglyceride levels as well as improving immunoparalysis of pancreatic tissue. After the acute management of HTGP, lifestyle modifications and oral agents such as fibrates, omega-3 fatty acids, and/or statins should be initiated to decrease triglyceride levels further and prevent the recurrence of acute pancreatitis. Awareness of recommended hospital management of HTGP is an important aspect of care for inpatient providers. Managing DM with or without insulin after discharge, along with dietary modifications may contribute to long-term improvements in triglyceride levels.

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Chapter 15

Type 3c Diabetes



Marina M. Charitou and Huda Al-Bahadili

Introduction

Type 3c diabetes is a form of secondary diabetes which occurs when primary pancreatic disorders damage the pancreatic islets of Langerhans leading to endocrine pancreatic dysfunction. The terms used to describe this unique type of diabetes include secondary pancreatic diabetes, diabetes of the exocrine pancreas, in addition to post-pancreatitis DM (PPDM). Interestingly, it is often misdiagnosed as Type 2 diabetes (or Type 1 diabetes); however, it differs in pathophysiology, clinical presentation, treatment, and degree of hyper- and hypoglycemia.

Epidemiology

The notion of diabetes in diseases of the exocrine pancreas has undergone a long evolution. Pancreatic diabetes was first reported by Harley in 1892 to denote the development of diabetes in animals after the removal of the pancreas. For decades, type 3c diabetes was considered a misnomer and was not recognized in any professional body in the field of diabetes [1] until the American Diabetes Association (ADA), together with the World Health Organization (WHO), defined this type of

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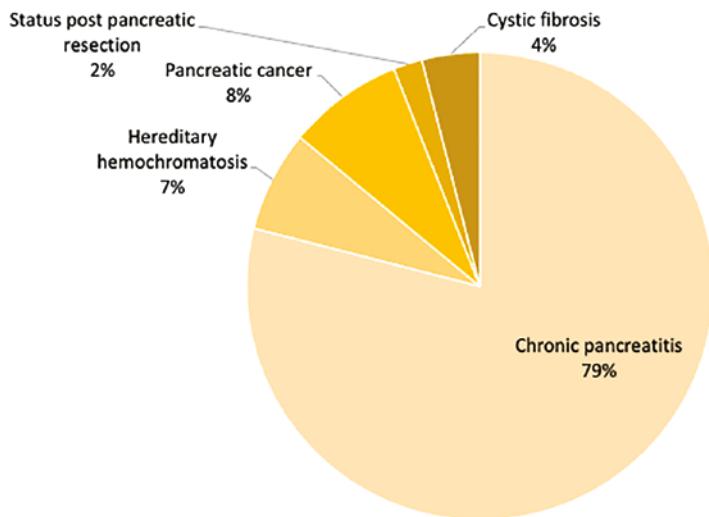


Fig. 15.1 Frequency of different causes of type 3c diabetes

diabetes in 2011 and was then incorporated as a category in the ADA guidelines in 2022. Type 3 DM is divided into 8 subtypes of which type 3c is the type associated with primary pancreatic disease [2]. The most commonly identified causes of type 3c diabetes are chronic pancreatitis, pancreatic ductal adenocarcinoma, hemochromatosis, cystic fibrosis, and previous pancreatic surgery (Fig. 15.1) [3]. The true worldwide prevalence of type 3c diabetes is unknown; nevertheless, it is reasonable to assume that the prevalence probably ranges from 1% to 9% of patients with diabetes. Based on a US prevalence of 22 million in 2014, incidence was estimated to be at least 150,000 cases of type 3c diabetes, or approximately 0.5–1% of all patients with diabetes [4]. Diabetes and pancreatic cancer have a multifaceted relationship. Long-standing diabetes mellitus is considered a risk factor for the development of pancreatic cancer. The time duration taken to define new-onset diabetes mellitus (NOD) in the context of pancreatic cancer (PC) is between 2–3 years. On the contrary, when diabetes is present for more than 2–3 years before the diagnosis of pancreatic cancer, it is considered to be long-standing T2DM. The evidence of association between NOD and PC is consistent; however, the evidence for risk of development of pancreatic ductal adenocarcinoma (PDAC) which is the most common form of PC is mixed. Moreover, the risk is cumulative and consistently increases from normal glucose tolerance to prediabetes to diabetes [5].

Pathophysiology

While insulin insufficiency is the cornerstone of this type of diabetes, there are inherent differences in the pathophysiology depending on the subtype of diabetes in this category [6]. In patients with type 3c diabetes, the pancreatic acinar cells and islets of Langerhans are impaired and/or destroyed by glandular inflammation and

fibrosis, resulting in cycles of hypo- and hyperglycemia due to loss of functional alpha and beta cells. Furthermore, hepatic insulin resistance and impaired gluconeogenesis may result from loss of pancreatic polypeptide cells. Mechanisms of hyperglycemia secondary to chronic pancreatitis are attributed to potential immunopathogenesis and hepatic insulin resistance. Potential immunopathogenesis was suggested by increased circulating leukocyte MMP9 which could indicate developing inflammation and/or persistent injury leading to immune cell recruitment. Another etiology of hyperglycemia related to chronic pancreatitis is hepatic insulin resistance which occurs when the number of available hepatic insulin receptors is decreased, and the internalization of hepatocyte plasma membrane GLUT2 is impaired. Additionally, nutrient maldigestion leads to an impaired incretin secretion and therefore a diminished insulin release from the remaining beta cells. Glucagon-secreting alpha cells and pancreatic polypeptide-secreting cells are also subject to destruction in chronic pancreatitis leading to a complex deranged metabolic situation comprised of frequent episodes of hyper- and hypoglycemia [7].

In the case of pancreatic cancer, the mechanism of hyperglycemia is also secondary to potential immunopathogenesis. Rather than increased leukocyte MMP9, elevated iS100A8/9 complex can be found. This complex is known to induce monocyte/macrophage TNF- α , which may not only augment the inflammatory cycle but release cytokines which can lead to β -cell dysfunction and apoptosis. Peri-islet macrophages, as they are modulated by cancer-derived exosomes, can internalize exosomes derived from cancer and non-cancer cells; however, only cancer-derived exosomes lead to macrophage secretion of pro-inflammatory cytokines and chemokines implicated in β -cell dysfunction [4].

The one subtype where etiology is complex but somewhat better understood is cystic fibrosis-related diabetes (CFRD). It is primarily related to insulin insufficiency which is present in essentially all patients with CF and is linked to collateral damage to the islets as exocrine tissue is destroyed. Other factors include chronic inflammation and peripheral insulin resistance. Pancreatic pathology starts with the abnormal chloride channel function resulting in thick viscous secretions and obstructive damage to the exocrine pancreas, progressive fibrosis, and fatty infiltration. This ultimately leads to disruption and destruction of islet architecture and loss of beta, alpha, and pancreatic polypeptide cells. In addition, patients with CFRD are modestly insulin resistant with both decreased peripheral glucose uptake and poor insulin-mediated suppression of hepatic glucose production. Insulin resistance is not as important as insulin deficiency in pathogenesis of CFRD, but it assumes a greater role during periods of stress such as acute pulmonary disease from infectious exacerbations and use of glucocorticoids [8]. For a detailed discussion focused on CFRD, please see Chap. 16.

The least common subtype of type 3c diabetes is pancreatic resection leading to what is commonly known as post-pancreatectomy diabetes. This etiology has a more straightforward pathophysiology which is dependent on the degree of pancreatic tissue removed and the type of surgery performed. It can influence the probability of developing pancreatogenic diabetes, as can a patient's preoperative diabetes status. Distal pancreatectomy (DP) confers a higher risk of developing post-pancreatectomy diabetes than pancreateoduodenectomy (PD) [9].

Clinical Manifestations

Pancreatic exocrine insufficiency usually pre-dates endocrine insufficiency. Most patients with type 3c diabetes have a known history of pancreatitis, abdominal pain, steatorrhea, or maldigestion with nutritional deficiencies requiring pancreatic enzyme replacement therapy and glucose intolerance. Patients may also present with symptoms of maldigestion and/or abdominal pain without a prior diagnosis of chronic pancreatitis, or may be asymptomatic except for glucose intolerance or diabetes, and only through careful clinical evaluation is pancreatic disease suspected. The alterations in glucose metabolism begin as asymptomatic or mild hyperglycemia early in the course of endocrine insufficiency, and periods of glucose intolerance may only be evident during stress, illness, or high-dose glucocorticoid treatment. Later in the disease course, there is often progression to brittle diabetes characterized by marked glycemic lability and frequent hypoglycemia. As opposed to type 1 DM, diabetic ketoacidosis is rare, most likely due to the persistence of some degree of endogenous insulin secretion and impaired glucagon secretion [10]. CFRD develops insidiously and may present during episodes of pulmonary infections/exacerbations, use of glucocorticoids and/or continuous nighttime drip feedings. Symptoms may include unexplained polyuria, polydipsia, failure to gain or maintain weight despite nutritional intervention. On the other hand, the symptoms of progressive weight loss or anorexia despite adequate glycemic control should alert the clinician for the possibility of PDAC [5]. Furthermore, in some instances, patients may be asymptomatic.

Definitions and Diagnosis

Distinguishing type 3c diabetes from type 1 or type 2 can present a diagnostic dilemma (Table 15.1). Type 3c diabetes is complex as it includes several pancreatic diseases with differing pathophysiology. There are no universally accepted

Table 15.1 Biochemical characteristics of different types of diabetes [6]

| Parameter | Type 1 | Type 2 | Type 3c |
|--|---|----------------|-----------------------------------|
| Fasting C-peptide (0.5–2.0 ng/mL) | Very low: <0.2 ng/mL | Normal to high | Low to normal |
| Ketoacidosis | Common | Rare | Rare |
| Hypoglycemia (glucose <69 mg/dL) | Common | Rare | Frequent |
| Islet autoantibodies | Positive | Negative | Negative |
| Exocrine insufficiency (fecal elastase <200 mcg/g) | Negative | Negative | Positive |
| CGMS (Continuous Glucose Monitoring system) | Hyperglycemia and reactive hypoglycemia | Hyperglycemia | Alternate hyper- and hypoglycemia |

diagnostic criteria for type 3c diabetes; however, Ewald and Bretzel proposed a criteria to aid with diagnosis (Table 15.2). According to the ADA, in addition to standard criteria for diagnosing diabetes, diagnosis of type 3c diabetes requires the presence of pancreatic insufficiency, evidence of pathologic pancreatic imaging and the absence of type 1 diabetes-associated autoimmune markers. Hence, while both type 1 and 3c DM have diminished insulin secretion, one absolute distinguishing feature of type 1 DM is the autoimmune destruction of the pancreatic islet cells as part of the disease process.

Misclassification of these patients is very common, yet identification of these patients is very important due to special diagnostic and therapeutic considerations in this subset of patients [12]. Pancreatic insufficiency is considered through history-taking (steatorrhea and diarrhea) and diagnosed with a low fecal elastase level (<200 mcg/g). Islet-specific autoantibodies can be studied through serum to assess for autoimmune type 1 diabetes. Additionally, beta-cell function can be evaluated via testing fasting C-peptide and stimulated C-peptide (C-peptide response to arginine or glucagon bolus). Of note, C-peptide is used instead of insulin because it is produced in equimolar quantities to endogenous insulin and is more stable in the serum. HbA1C can be used to provide a global understanding of average glucose level although it will not provide a good representation of the severity of blood glucose variability. For patients with CF, guidelines state that A1C should not be used as a diagnostic tool for CF-related type 3c diabetes. Instead, oral glucose tolerance test (OGTT) is the screening and diagnostic test of choice [9]. An additional and alternative test which is considered a specific indicator of type 3c diabetes is an absent pancreatic polypeptide response to mixed-nutrient ingestion. Apart from beta cells, alpha cell dysfunction is present and manifests as impaired glucagon production, however due to substantial heterogeneity of glucagon in the serum, glucagon levels cannot be accurately assessed by serum studies. Regarding patients undergoing pancreatic resection, Maxwell et al. developed a validated scoring index that preoperatively predicts the development of diabetes after pancreaticoduodenectomy and

Table 15.2 Ewald and Bretzel proposed diagnostic criteria for type 3c diabetes [11]

| |
|--|
| Major: |
| 1. Exocrine pancreatic insufficiency (by monoclonal fecal elastase-1 testing or direct function tests) |
| 2. Consistent pancreatic abnormalities on imaging (endoscopic ultrasound, MRI, or CT scan) |
| 3. Absence of related autoimmune markers of type 1 diabetes |
| Minor: |
| 1. Impaired β-cell function (as measured by homoeostatic model assessment for β-cell function, or C-peptide or glucose concentrations) |
| 2. Absence of insulin resistance (as defined by homoeostatic model assessment for insulin resistance) |
| 3. Impaired incretin secretion (glucagon-like peptide-1 [GLP-1] or pancreatic polypeptide, or both) |
| 4. Low serum concentrations of lipid-soluble vitamins (A, D, E, and K) |

distal pancreatectomy (Fig. 15.2) [13]. In addition, continuous glucose monitoring systems (CGMS) can provide highly accurate, ongoing surveillance of glucose levels and can be clinically useful in identifying periods of hyperglycemia and hypoglycemia in pancreatogenic diabetes [14]. It has been validated for use in children, adolescents, and adults with CF as a valuable tool to diagnose early glucose tolerance abnormalities. Furthermore, CGM is being studied as a predictor of islet function following pancreatic surgery and autologous islet transplant. CGMS offers more complete data on low blood glucose incidents, including symptom-free hypoglycemia, than intensive blood glucose monitoring with the use of a glucose meter [15].

In addition to biochemical testing, imaging of the pancreas can provide additional diagnostic clues. MRI is the preferred imaging modality to diagnose pancreatic disease such as chronic pancreatitis and pancreatic cancer. CT of the abdomen can also be highly sensitive for identifying abnormal pancreatic parenchyma or masses. When type 3c diabetes is due to chronic pancreatitis, pancreatic calcifications on abdominal imaging can be a helpful clue [4].

Management

Identification of type 3c diabetes is crucial for recommending an appropriate treatment plan for both inpatient and outpatient settings. For example, patients with type 2 diabetes may be prescribed oral hypoglycemic agents at discharge which would be inappropriate and inadequate for patients with type 3c diabetes. Here, our chapter focuses on inpatient management of type 3c diabetes. While there is no evidence-based treatment for type 3c diabetes that is uniquely distinguished from types 1 or 2 diabetes, treatment should be based on the disease's cause and pathophysiology. The course of the disease is complicated by maldigestion and concomitant qualitative malnutrition which make the management of type 3c diabetes very complex [16]. Principles of management include preventing hypoglycemia and

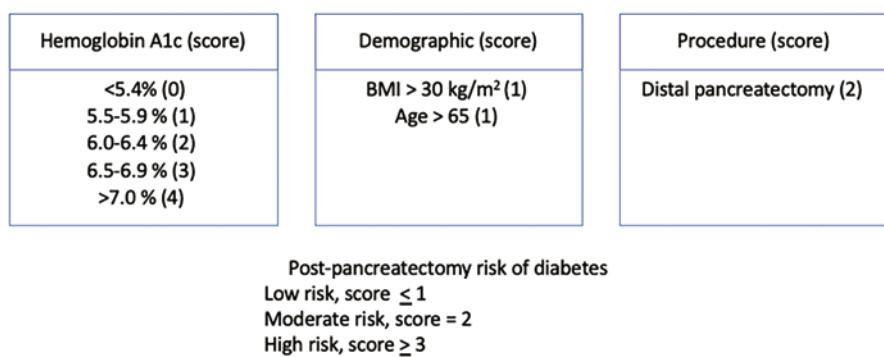


Fig. 15.2 Post-pancreatectomy Diabetes Index (PDI) [13]

hyperglycemia, while avoiding exacerbation of malnutrition by maintaining appropriate meal plans such as small and frequent meals. Patients should monitor glucose frequently, ensure adequate pancreatic enzyme replacement therapy and have routine dietitian assessment [17]. Furthermore, the derangement in glucose metabolism in type 3c diabetes mellitus ranges from a mild to severe impairment, characterized by frequent episodes of hypoglycemia which can result from loss of glucagon response to hypoglycemia, carbohydrate malabsorption, and/or inconsistent eating patterns due to concomitant pain and/or nausea. Therefore, patients shall be treated with specifically tailored medical nutrition and pharmacologic therapies [10].

Insulin is the mainstay medical therapy for type 3c diabetes in both the inpatient and outpatient settings. As published by Moran et al., the ISPAD Clinical Practice Consensus Guidelines from 2018 discussed the management of patients with CFRD in their usual state of health, during stress, as well as in association with overnight drip feeding [9]. It was suggested that patients typically require up to 0.5–0.8 units of insulin per kg body weight per day when they are in their usual state of health. Much more may be required during stress. Due to the catabolic effects of insulin insufficiency, the goal is to give the patient as much insulin as can be safely tolerated. For basal insulin, the goal is approximately 0.25 unit per kg body weight per 24 h; start at half this and adjust upward based on fasting glucose levels. Regarding prandial rapid-acting insulin dosing, use of insulin to carb ratio (ICR) and insulin sensitivity with a correction scale are considered standards of care. Start with 0.5–1 unit rapid-acting insulin for every 15 g of carbohydrate consumed. While pre-meal dosing is always preferred, it is acceptable to consider administering rapid-acting insulin doses immediately after the meal in those who are unsure what or how much they will eat due to nausea or gastroparesis. In addition to ICR, pre-meal correction is recommended and is usually started at 0.5–1 unit rapid-acting insulin for every 50 mg/dL above 150 mg/dL and adjusted as needed. In certain instances, patients with pancreatogenic diabetes may require overnight drip feeding which frequently is covered by a single dose of regular insulin plus NPH (e.g., Humulin N, Protaphane, Novolin N, Insulatard, Isophane) insulin. The regular insulin covers the first half and the NPH the second half of the feeding. A starting insulin dose is determined by identifying the total grams of carbohydrate in the feeding, determining a total insulin dose based on the ICR (typically 0.5–1 units per 15 g), and delivering half of this as regular and half as NPH insulin. Glucose levels 4 h into the feeding are used to adjust the regular insulin dose and those at the end of the feeding to adjust the NPH insulin dose. Think of this as a “long meal,” it does not replace basal insulin, and patients should only take this insulin when they have the overnight feeding [9]. For patients on tube feeding, blood glucose monitoring is recommended every 4 h.

As mentioned above, patients with type 3c diabetes are at higher risk of hypoglycemia where severe events are known to be associated with a 3.4-fold increase in 5-year mortality [18]. The ADA does not classify specific targets for glycemic control for patients with type 3c diabetes, nor does it define a safe value for A1C [11]. However, ADA defines stages of hypoglycemia that may be especially crucial to identify in a patient with type 3c diabetes (T3cDM):

- Level 1 is defined as glucose between 54 and 69 mg/dL
- Level 2 is defined as glucose less than 54 mg/dL
- Level 3 (severe hypoglycemia) is defined as glucose less than 54 mg/dL requiring assistance

Blood glucose levels should be monitored regularly. A blood glucose level of <70 mg/dL should always be treated, even if the patient is asymptomatic. For patients with T1DM and T2DM on intensive insulin regimens, the ADA has recommended inpatient blood glucose monitoring 4 times a day, before each meal and at bedtime for those who are eating. While T3cDM was not discussed, these recommendations could be extrapolated for those with T3cDM on intensive insulin regimens [19]. The usefulness of continuous glucose monitoring system (CGMS) in the detection of hypoglycemic episodes in patients with diabetes secondary to chronic pancreatitis was investigated. It was found that CGMS offers more complete data on low blood glucose incidents, including symptom-free hypoglycemia, than intensive blood glucose monitoring with the use of a glucose meter [15]. Studies have shown that closed-loop insulin pumps have been successfully used peri-operatively in individuals undergoing pancreatic resection, achieving glycemic control without hypoglycemia. The use of a low-glucose suspend sensor-augmented insulin pump or continuous subcutaneous insulin infusion (CSII) facilitates intensive insulin therapy while avoiding the pitfalls of hypoglycemia. Therefore, low-glucose suspend sensor-augmented CSII should be considered as a viable treatment option for people post-pancreatectomy [20]. For CFRD, diabetes technology is increasingly being used. Scully et al. studied the impact of hybrid closed loop (HCL) technology on glycemia in this patient population. They found that Control IQ initiation was associated with a significant increase in % time in target range (70–180 mg/dL), as well as decreases in average glucose, % time in hyperglycemic ranges (% time >180 mg/dL, % time >250 mg/dL), and glycemic variability (standard deviation, coefficient of variation). There was no significant change in % time in hypoglycemia ranges (% time <54 mg/dL, % time <70 mg/dL) [21]. Aside from insulin therapy, autologous islet transplant is a noteworthy procedure which was found to mitigate the severity of type 3c diabetes and prevent post-operative diabetes in up to one-third of patients. It is a surgical procedure in which the pancreas gland, following resection, is digested to isolate the islet cells and then be infused into the patient's liver. Islet autotransplantation is indicated when total pancreatectomy is required for the treatment of recurrent acute or chronic pancreatitis associated with frequent debilitating exacerbations and/or chronic, unrelenting pain [22].

Conclusion

Type 3c diabetes is a form of secondary diabetes due to non-autoimmune primary pancreatic disorders leading to endocrine pancreatic dysfunction. It is often misdiagnosed as Type 2 diabetes (or Type 1 diabetes); however, it is remarkably different

in underlying etiologies, clinical presentation, and treatment. Given insulin insufficiency is the cornerstone of this disease, insulin is the mainstay therapy in inpatient and outpatient settings. In addition, close monitoring of patients with type 3c diabetes is essential as they are more prone to experience complications and death related to severe hypoglycemic events.

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Chapter 16

Cystic Fibrosis-related Diabetes



Ryan Richstein, Trisha Menon, and Janice Wang

Introduction

Cystic fibrosis (CF) was first described in 1938 in postmortem infants who were malnourished and demonstrated pancreatic fibrosis on autopsy [1]. CF is a rare autosomal recessive genetic disorder in which mutations in the CF gene located on chromosome 7 (7q31.2) result in protein defects in the cystic fibrosis transmembrane conductance regulator (CFTR), a cAMP protein kinase chloride ion channel that regulates chloride and bicarbonate transport in epithelial cells of the airway, submucosal glands of the pancreas and intestine, and sweat glands. This results in thick mucus production in mucin-producing glands, causing obstruction and hyperinflammation on the cellular level and subsequent organ injury. While respiratory manifestations include bronchiectasis and chronic lung infections, other organ systems affected by CF include the exocrine and endocrine pancreas, the sinuses, the gastrointestinal system, the liver, and reproductive system.

There are currently over 32,000 people with CF (PwCF) registered in the United States CF Foundation (CFF) Patient Registry [2]. There remains no cure for CF. Mortality is commonly related to respiratory failure; however, other comorbidities can influence prognosis. In 1954, the median survival age was 5 years old. By the 2010s, the CF community observed benefits from advancements in early

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diagnosis, standardized care with anti-infective inhalational therapies, pancreatic replacement enzyme therapies, and the first CFTR modulator called ivacaftor (Kalydeco®). Ivacaftor is a potentiator of the CFTR and improves chloride transport. The most recent CFTR modulator to become commercially available is elexacaftor/tezacaftor/ivacaftor (ETI, also known as Trikafta®), which is a combination of two CFTR protein correctors (elexacaftor and tezacaftor) plus ivacaftor. ETI is a highly effective modulator treatment (HEMT) associated with reduced pulmonary exacerbations (Pexs), improved lung function and weight gain in patients with eligible CF mutations. Nearly 90% of the CF population are eligible for ETI which are mostly those carrying at least one copy of the most common CF mutation, F508del. CF is no longer considered a pediatric disease as more than half of the CF population is of adult age. The median predicted survival for PwCF born between 2017 and 2021 is now 53 years of age [3]. Chronic and new long-term comorbidities in the aging CF population should be considered when caring for PwCF. Of great importance is CF-related diabetes (CFRD) and its immediate- and long-term health impact. In this chapter, we review the pathophysiology of CFRD, diagnosis, and treatment with a focus on inpatient management.

Pathophysiology of Cystic Fibrosis-related Diabetes

CFRD results from a disruption in the pancreatic endocrine function and is a form of Type 3C diabetes mellitus (DM) that incorporates aspects of both Type 1 (T1DM) and Type 2 DM (T2DM) [4]. CFRD results predominantly from reduced insulin secretion due to beta cell destruction and dysfunction, similar to that seen in T1DM; however, it is not antibody mediated [4]. Reduced insulin sensitivity, which commonly develops in the pathogenesis of T2DM, is not as apparent in CFRD but may develop over time [4].

Hyperglycemia in CFRD results from alterations in both alpha and beta cell function [5]. In the beta cell, CFTR protein dysfunction causes lower intracellular chloride levels, thereby inhibiting depolarization in response to glucose levels that would normally trigger insulin release; this leads to requiring higher levels of glucose to stimulate insulin release [6]. Additionally, CFTR dysfunction decreases intracellular insulin vesicle trafficking for release following depolarization, resulting in further decrease in insulin secretion [7].

Studies have shown that beta cell destruction is also a key factor in the pathogenesis of CFRD. CFTR dysfunction reduces secretory volume and increases protein concentration in pancreatic ducts. These thickened secretions cause duct obstruction and interstitial edema, with accumulation of zymogens in the acini that digest pancreatic tissue, leading to beta cell destruction. The “Bystander Theory” describes exocrine dysfunction which ultimately leads to beta cell destruction [8].

In the alpha cell, CFTR regulation of chloride entry also causes cell hyperpolarization and inhibits glucagon secretion. With CFTR dysfunction, low intracellular concentrations of chloride stop the inhibition of glucagon release, thereby

increasing alpha cell glucagon release, leading to hyperglycemia [9]. Impaired insulin secretion also decreases glucagon inhibition, further increasing glucagon release [9]. Contrary to CFRD, other forms of Type 3C diabetes have diminished glucagon production and release due to generalized destruction of pancreatic cells, including alpha cells [10]. In CFRD, as alpha and beta cell dysfunction continues, the destruction of these cell types is also occurring due to exocrine pancreas defects as mentioned earlier. It is unclear when that alpha cell destruction will be enough to see decreases in glucagon secretion similar to that in other forms of Type 3C, as studies on glucagon action in CFRD are limited [11].

As mentioned, CFTR is important in beta cell depolarization and insulin release. First phase insulin release occurs in response to nutrient exposure, which may explain why post-prandial hyperglycemia is more common than fasting hyperglycemia in patients with CFRD [12]. Another contributor to post-prandial hyperglycemia in CFRD is fat maldigestion. Fat maldigestion leads to rapid gastric emptying and reduced gastric inhibitory polypeptide (GIP) and glucagon-like peptide (GLP-1), which both stimulate insulin release in the presence of glucose. Glucose is typically introduced to the body with meals, and with decrease in GIP and GLP-1, insulin will not be released in response to the glucose load from meals, leading to post-prandial hyperglycemia [13]. Understanding the pathophysiology of CFRD development is helpful in determining new management options.

Diagnosis of Cystic Fibrosis-related Diabetes

CFRD is the most frequent comorbidity of CF and involves more than 40% of patients older than 30 years [4]. Pulmonary and nutritional deterioration begins 2 to 5 years prior to CFRD diagnosis [5]. Certain risk factors for CFRD include certain genotypes, pancreatic insufficiency, and female gender. Classes I and II CF mutations increase the risk of developing CFRD independent of other known risk factors and have been associated with worse clinical disease [4]. Classes IV, V, and VI mutations, on the other hand, typically have less severe phenotypes than Classes I and II mutations and are associated with a lower risk for CFRD [4]. Additionally, the presence of a CF pancreatic disease marker, immunoreactive trypsinogen (IRT), declines as pancreatic damage occurs [5]. Lower levels of IRT are associated with severe CFTR genotypes and increased CFRD risk [5]. Less severe mutations may not warrant screening until later in age; however, there are thousands of CFTR mutations and not all mutations are known in PwCF. Thus, due to the multifactorial risks associated with CFRD, current guidelines recommend CFRD screening irrespective of mutation class [4].

Most CF patients have no clinical signs or symptoms of hyperglycemia at the time of diagnosis [4]. The American Diabetes Association (ADA) screening guidelines for CFRD are stricter than those for T2DM because disruptions in glucose homeostasis start early in life [4]. Annual recommended screening starts at age 10 using the oral glucose tolerance test (OGTT) [4]. During a period of stable baseline

health, CFRD can be diagnosed according to standard ADA criteria (2-h OGTT glucose ≥ 200 , or fasting plasma glucose ≥ 126 mg/dL). Testing should be confirmed on two different days unless the patient is having symptomatic hyperglycemia (polyuria, polydipsia) with a glucose ≥ 200 [3].

The OGTT is the test of choice when performing annual screenings for CFRD. Hemoglobin A1c (HbA1c) is not sensitive in CFRD diagnosis since it is often low in PwCF and a value less than 6.5% does not exclude CFRD. HbA1c, however is useful in monitoring CFRD [3, 4]. After a minimum 8-h fast, an OGTT is performed by drinking 1.75 g per kilogram body weight in 250–300 mL of glucose, with a maximum amount of 75 g of glucose over 5 min [4]. The blood glucose is measured before administration, and at 60 and 120 min after drinking a glucose load. No physical activity or other tests are to be performed during the OGTT. The results of the OGTT can be classified as follows: normal glucose tolerance (NGT), fasting hyperglycemia (FH), impaired glucose tolerance (IGT), indeterminate glycemia (INDET), CFRD without FH, and CFRD with FH (Table 16.1) [4].

Different circumstances require adjustments in screening timelines and cutoffs. If planning pregnancy or undergoing organ transplantation, OGTT should be performed if prior results were abnormal, or if an OGTT was not performed within the past 6 months [3]. Gestational diabetes mellitus screening is recommended at both 12–16 weeks and 24–28 weeks with an OGTT, and if diagnosed, OGTT is repeated at 6–12 weeks postpartum [3]. Ideally, CFRD should be diagnosed when patients are at baseline health status; however, Pexs are risk factors for poorly controlled hyperglycemia that may persist beyond the Pex duration. Patients may indeed meet criteria for CFRD during or following a Pex and benefit from insulin therapy. In patients without a known diagnosis of CFRD and required hospitalization for a Pex, hyperglycemia as defined by ADA criteria on OGTT was very frequent in a small pediatric study of 9 patients (2 with new CFRD and 6 with abnormal OGTT) [14]. The trajectory of glucose tolerance improved with initial Pex treatment however, following return to respiratory baseline and clinical outpatient visit, refractory hyperglycemia was observed at a median duration of 3.8–6.3 months [14]. For this reason, assessment of hyperglycemia should not end with Pex treatment but should be re-evaluated upon return to clinical respiratory baseline. CFRD may be diagnosed with fasting plasma glucose concentrations (FPG) of ≥ 126 mg/dL or 2-h post-prandial plasma glucose of ≥ 200 mg/dL for more than 48 h [3]. Patients using enteral nutrition with mid- or post-feeding glucose values of ≥ 200 mg/dL on two

Table 16.1 Classification of results in the oral glucose tolerance test (OGTT) in CFRD [4]

| | Blood glucose (mg/dL) | | |
|---|-----------------------|------------|------------|
| | Start | 60 min | 120 min |
| Normal glucose tolerance (NGT) | <100 | <200 | <140 |
| Impaired glucose tolerance (IGT) | <126 | <200 | 141–199 |
| Indeterminate glycemia (INDET) | <126 | ≥ 200 | <140 |
| CFRD without fasting hyperglycemia (FH) | <126 | – | ≥ 200 |
| CFRD with FH | ≥ 126 | – | ≥ 200 |

separate days meet diagnostic criteria for CFRD. It is important to note that if these values are obtained using self-monitoring of blood glucose via capillary blood, values need to be confirmed by laboratory plasma testing in order to make the diagnosis of CFRD.

The OGTT is the gold standard screening tool; however, the emergence of continuous glucose monitoring (CGM) has demonstrated promise in more accurate predictions of glucose trends and development of CFRD. Recent studies have demonstrated that the ability of CGM to detect glycemic variability during basal and post-prandial settings over several days improved the chances of diagnosing CFRD earlier, whereas the diagnosis would have been missed with OGTT screening [5]. Continuing advances in the detection of CFRD is crucial in curbing the complications of uncontrolled CFRD.

Complications and Outcomes of Cystic Fibrosis-related Diabetes

CFRD has been associated with a higher mortality risk; however, studies have noted that the mortality gap between patients with and without CFRD has narrowed, likely due to earlier detection and more aggressive management of CFRD and CF. [4, 15] Female gender was also associated with increased mortality, but sex differences are now not as clear [4]. Trends in the incidence and prevalence of CFRD will need to be re-analyzed in the era of HEMT as the landscape of CF as a disease is changing and survival is improving. Also, multi-organ injuries are likely to be less pronounced since CFTR modulator therapy is being prescribed to the pediatric population as young as 1 month old.

CFRD is a known risk factor for worsening pulmonary function. A 4-year prospective study of CF patients with various glucose profiles following an OGTT demonstrated the greatest decline in lung function (measured by forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV1)) in those with CFRD compared to those with normal glucose tolerance and impaired glucose tolerance [16]. In all patients with diabetes, regardless of type, pulmonary capillary blood volume, lung elastic recoil, FVC and FEV1 are all diminished, with a concomitant increase in basal lamina thickness and increased collagen/elastin deposition, all of which leads to poor alveolar air diffusion [5]. These changes are partly a result of increased glucose in the airway surface liquid (ASL), causing cytokine release and damage to lung tissue [17]. Typically, the glucose threshold for when increased glucose appears in the ASL is 144 mg/dL, which is well below the CFRD diagnostic criteria of 200 mg/dL [17]. While PwCF have lung infections due to poor airway clearance and thickened secretions, elevated glucose in the ASL further exacerbates the rate of infections since pathogens have more glucose substrate to thrive on [17].

Proper nutritional status is essential for optimizing pulmonary function in PwCF. Insulin deficiency causes catabolism of proteins, which compromises nutritional status and decreases pulmonary function, thereby increasing morbidity and

mortality [18]. In adults aged 21–40 years, a body mass index (BMI) of 22 in females and 23 in males was associated with optimal FEV1 [18]. Insulin therapy is the gold standard in CFRD treatment as a means to replenish insulin insufficiency. Increased insulin decreases catabolism and may even serve as an anabolic agent through glucose utilization although data on this is limited. Additionally, insulin increases appetite and serves in the reward centers in the hypothalamus, thereby further increasing food intake and weight gain [19]. Nutrition optimization is also essential to improving survival in PwCF and CFRD.

Similar to other forms of diabetes, CFRD is associated with microvascular complications, with 14% developing microalbuminuria and 16% with retinopathy [4]. CFRD patients have increased rates of nephropathy compared to T1DM and T2DM patients, but tend to develop microvascular complications later [4]. Interestingly, CFRD patients do not develop macrovascular complications, but these may become more apparent as the lifespan of these patients continues to increase. Unlike T1DM patients who develop ketoacidosis in the setting of insulin deficiency, CFRD patients often do not, likely secondary to residual insulin secretion in the earlier stages. As ongoing destruction of beta cells occurs, however, the risks of DKA increases [20]. HbA1c goals should be lower in CFRD patients compared to other diabetes groups because HbA1c does not correlate well with glucose values in this population. A prospective observational study demonstrated a three-fold increased risk of death when the HbA1c was $\geq 6.5\%$. However, there is no established HbA1c goal to prevent microvascular complications in CFRD [4]. Screening for CFRD and its associated complications are essential to the prevention of future comorbidities.

Management of CFRD

Decline in pulmonary and nutritional status in CFRD patients is typically observed years before CFRD is diagnosed. Elevation in airway glucose levels leads to bacterial infections [5]. When controlling for disease severity, PwCF and CFRD are more likely to have worse mortality compared to those with CF without CFRD [21]. Specifically, in patients with CFRD greater than 30 years of age, mortality is 1.8 in 100 person-years, compared to 0.5 in those with CF without CFRD [22]. The paramount long-term goal in CFRD treatment is reduction of morbidity and mortality associated with dysglycemia.

Nutrition and Exercise Considerations

The approach to dietary management of CFRD diverges from the typical recommendations given to patients with T1DM and T2DM. Caloric restriction and weight loss are recommendations in T2DM and sometimes in T1DM. These measures, however, are not applicable to patients with CFRD as they do not halt disease

progression, characterized primarily by insulin deficiency rather than insulin resistance. T2DM dietary restrictions are often unknowingly recommended to CF patients by medical providers unfamiliar with the nutritional needs of PwCF and CFRD [21]. Due to increased baseline metabolic demand and exocrine pancreatic insufficiency, PwCF are generally encouraged to consume more daily calories than the general population [23]. This includes regular meals and frequent snacking, with an emphasis on high calorie, high salt, high fat, and regular or even liberal carbohydrate intake. Carbohydrate counting becomes especially important in those using insulin therapy. PwCF can experience variable appetite and PO intake, thus an optimal insulin dosing strategy may emphasize dosing based on actual carbohydrate intake rather than using pre-determined prandial insulin dosing. Physical exertion and illness also influence insulin requirements, necessitating adjustments to regimens. Similar to other types of DM, regular exercise is recommended in CFRD as it lessens the frequency of blood glucose spikes, especially after meals [21]. This is thought to be due to improved insulin sensitivity, even though glucose insensitivity is not a key feature of CFRD [24]. As a result, exercise can theoretically increase the risk of hypoglycemia, so patients may need to snack or reduce insulin doses prior to or after exertion.

Insulin

According to the CFF CFRD clinical care guidelines, insulin is the only recommended treatment for CFRD, as there is insufficient data to recommend other agents [21]. The CFF Patient Registry Annual Data Report of 2020 revealed that 71.4% of PwCF and CFRD in the United States were treated with chronic insulin compared to other therapies (Table 16.2) [2]. Worldwide, approximately 75% of CFRD patients use insulin [4]. Benefits of insulin therapy in CFRD include reducing ASL glycemic content and associated pulmonary sequelae of pulmonary infections and lung function deterioration, and the nutritional sequela of weight loss. Insulin has anabolic effects, countering the catabolic loss of muscle mass and protein stores in CFRD patients, thus insulin therapy can improve weight gain [5, 21]. Insulin use appears to confer a comparable risk of hypoglycemia, albeit less severe in the CFRD population than in T1DM patients [5].

Table 16.2 Treatment approaches for people with cystic fibrosis-related diabetes (CFRD) [2]

| Therapy for CFRD | People with CF on therapy (not mutually exclusive) |
|--|--|
| Nutritional intervention | 21.2% |
| Oral DM agents | 4.0% |
| Chronic insulin | 71.4% |
| Intermittent insulin (in setting of illness, steroids, etc.) | 4.6% |
| No treatment | 13.3% |

Table 16.3 Insulin regimens based on varying clinical scenarios [21]

| Clinical scenario | Suggested insulin regimen |
|--------------------------|------------------------------------|
| Fasting hyperglycemia | Basal insulin and prandial insulin |
| No fasting hyperglycemia | Prandial and/or basal insulin |

Insulin regimens should be individualized; no regimen of basal, bolus, or a combination thereof has been proven superior to another for the general CFRD population (Table 16.3) [21]. For a patient with fasting hyperglycemia—a finding that tends to occur years after the onset of CFRD—long-acting basal insulin such as insulin glargine is reasonable, with rapid-acting prandial insulin. Some patients without fasting hyperglycemia can be managed effectively with just prandial insulin boluses, such as insulin lispro or aspart with meals or snacks [21, 25]. However, the 2022 ISPAD guidelines suggest that in young patients without fasting hyperglycemia with frequent small meals or snacks, basal insulin alone may be successful in controlling glucose levels [26]. Regular meals and snacks may lead one to expect that rapid-acting insulins would be most efficacious in controlling BG (blood glucose) excursions, but data has not borne this out [5]. A 2016 Cochrane review of randomized controlled trials comparing all methods of diabetes therapy in patients with CFRD, including rapid-acting versus long-acting insulin regimens, showed no one regimen was decisively more effective than any other in achieving euglycemia and countering deleterious effects of CFRD [27]. For the analysis, 22 trials were considered but only four were ultimately included. Only one directly compared long- and short-acting insulin, and all four of the trials had limitations.

Mixed insulins containing intermediate-acting NPH insulin and short-acting regular insulin have been used successfully in CFRD although they have limitations that can make them less preferred. One dosing advantage of mixed insulin regimens in the DM (non-CF) population is twice-daily versus three- or four times-daily regimens. This twice-daily simultaneous administration of both short- and intermediate-acting insulins is challenging for CFRD patients to use, as they cannot always effectively treat for frequent meals and snacks and are also at risk for hypoglycemia during periods of lesser carbohydrate intake.

Grover et al. demonstrated improved weight gain and fasting blood glucose levels in CFRD patients with fasting hyperglycemia using once-nightly dosing of glargine compared to once-nightly dose of NPH [21, 28]. When starting a patient with CFRD on insulin, it is important to remember that insulin resistance may not be present, especially in younger patients. Insulin sensitivity does tend to decline with age in patients with CFRD. It is prudent to start with conservative insulin dosing and titrate up as needed. Scheuing et al. reported that CFRD patients required more prandial insulin (~11% more) and less basal insulin (~29% less) overall when compared to patients with T1DM [21, 29]. On the other hand, Konrad et al. suggested that insulin requirements in adults with CFRD were no different than in adults with T1DM or T2DM [4].

In patients on multiple daily insulin injections, frequent finger-stick blood glucose (FSBG) monitoring, or use of CGM, is necessary for optimal care and

surveillance. Care should also be taken to rotate insulin injection sites to prevent adipose tissue overgrowth, known as lipohypertrophy, which tends to harden and impair insulin absorption. This is especially true in patients with CF as they tend to be slender and may have fewer areas with adequate subcutaneous fat in which to comfortably inject insulin. Affected areas must be allowed to heal before re-introducing insulin injections to previously used sites [21].

Insulin pumps are commonly used devices that are worn on the body and deliver insulin in small doses throughout the day and night. The pumps are programmed to provide insulin delivery at rates personalized to a patient's insulin needs at various times of day and during various activities such as exercise or sleep. They can also be used to deliver prandial boluses before meals and correction doses of insulin to cover hyperglycemia. Small studies in the CFRD population have shown improved blood glucose control with the use of insulin pumps, largely as a result of improved insulin coverage with meals and snacks [21]. Also, patients with CFRD are at risk of hypoglycemia due to frequent meals and snacks; insulin pumps can minimize this risk of insulin "stacking," when the lingering hypoglycemic effects of recent food coverage add to the effects of a new bolus [21].

Monitoring

Standard of care for monitoring BG in CFRD is self-monitoring of blood glucose (SMBG), requiring frequent and burdensome finger-sticks. CGM is a technology that allows for collection of a significantly more robust set of BG data for a given day, week, or month. With CGM, patients wear a small button-like sensor on the body surface that continually measures glucose levels in interstitial fluid. This continuous collection of glucose information allows patients and providers to make fine adjustments to a treatment regimen with real-time feedback. CGM data reports also provide the average sensor glucose value, and the glucose management indicator (GMI), a relative of the HbA1c but with less variability due to factors such as red blood cell half-life. A 2022 systematic review and meta-analysis demonstrated that CGM use for at least 6 weeks resulted in a 0.4% reduction in HbA1c compared to SMBG [30]. This is congruous with benefits seen in T1DM patients using CGM, a 0.26% reduction in HbA1c compared to SMBG. CGM also detects early dysglycemia that would otherwise be missed on a 2-h OGTT [31]. Hyperglycemia in CFRD is associated with worsening lung function (FEV1), weight and lung microbiome disruption, thus it is vital to diagnose and treat early. Use of insulin to treat hyperglycemia seen on CGM data has shown improvements in FEV1 and weight in CFRD patients [32]. At this time, there is insufficient data to recommend specific CGM BG targets. In T1DM, CGM use is associated with reduced anxiety related to hypoglycemia and improved general quality of life measures. CFRD patients also have favorable experiences with CGM, reporting that the devices are convenient and easy to use and would recommend future use [30]. To date, data comparing continuous monitoring strategies and impact on pulmonary and non-pulmonary outcomes

in CFRD is lacking. As with the greater diabetes mellitus population, getting insurance coverage for CGM devices remains problematic for some.

Inpatient-Specific Considerations in the Management of CFRD

Majority of reasons for hospitalizations in CF are related to pulmonary followed by gastrointestinal manifestations [33]. As expected, pulmonary manifestations are primarily related to moderate or severe Pexs which are commonly treated with intravenous (IV) antibiotics and sometimes the addition of corticosteroids. As Pexs pose a risk for hyperglycemia, dysglycemia also poses a risk for Pexs. CFRD comorbidity strongly influences risk for and outcome of hospitalizations in CF.

In one 2012 retrospective chart review descriptive study, 121 CFRD patients during 410 hospital admissions were studied. The study authors found that CFRD patients had a higher rate of hospitalization compared to PwCF without CFRD (3.4 times per patient versus 1.9 times per patient in 32 months). CFRD patients had a younger age of admission compared to PwCF without CFRD ($31.9 +/− 11$ years versus $34.8 +/− 13$ years). Seven patients with CFRD expired during the observation period compared with three PwCF without CFRD, consistent with other published mortality data, per the study authors [25].

Depending on the course of illness and/or clinical practice, Pexs may be fully treated while in-patient, or be transitioned to home IV antibiotics to be completed after hospital discharge if appropriate. The recovery phase may extend beyond the hospital stay and even past the course of IV antibiotics as full recovery is not always achieved quickly, if at all. This plays a role in continual follow-up in terms of CFRD. In a retrospective study of pediatric CF patients (mean age of 15.1; standard deviation of 3.3 years) who were hospitalized for a Pex and completed their IV treatment at home, poor glycemic control while inpatient was associated with lower lung function recovery compared to those with better glycemic control; similar trends were also observed at the end of treatment and at clinic follow-up.³³ In patients who completed their treatment course in the hospital, there were no significant differences in FEV1 recovery between well-controlled and poorly controlled hyperglycemia supporting benefit in in-patient treatment for those with poorly controlled CFRD [34]. Glycemic control likely influences illness and recovery phases from a Pex and may need to be considered when deciding between completion of treatment while in-patient versus outpatient.

Monitoring for hyperglycemia during a Pex requiring hospitalization is essential for CF patients with and even without CFRD. Patients may have undiagnosed CFRD or glucose intolerance that is revealed during a hospitalization. In real-world experiences, adherence to annual OGTT for PwCF is challenging. According to the U.S. CF Patient registry of 2021, completion of annual OGTT screening in PwCF without diabetes between “10 to 17 years old” and for those “18 years and older”

was a median of 60.6% and 28.7%, respectively [35]; this leaves an opportunity to detect glucose intolerance while in-patient, albeit during illness. Hospitalization, as a healthcare touchpoint, also provides an opportunity to provide education, therapy modification and guidance to patients with known or newly diagnosed CFRD who may not be well-established with an outpatient diabetes management team or who need interim adjustments.

Inpatient management of CFRD can be challenging as patients are acutely ill, can have unpredictable food intake, and may require steroid use. If insulin therapy is initiated in a previously non-CFRD patient during hospitalization, insulin requirements may fluctuate during recovery phase; multidisciplinary follow-up with endocrinology and CF care teams is important.

Data regarding inpatient treatment of CFRD is sparse. Based on general management recommendations for CFRD as described above, inpatient management of (non-CF) DM, as well as the experience shared in the previously mentioned 2012 large retrospective chart review descriptive study, a mindful, team-oriented approach can be recommended to optimize outcomes for PwCF who are hospitalized.

It is helpful to educate all team members caring for a PwCF that typical DM dietary restrictions are unlikely to apply, as most PwCF and CFRD require high caloric intake. Therefore the usual “carbohydrate consistent diet” typically ordered in the hospital for a patient with diabetes should not be ordered for a patient with CFRD. Any relative or health professional involved in the patient’s care should be made aware of these recommendations, as patient reception of conflicting information can lead to frustration and mistrust.

As discussed, there is no one insulin regimen that has been proven superior in CFRD. In the 2012 retrospective chart review descriptive study referenced above, patients were treated with insulin during the large majority of admissions (87.6% of all admissions), and of those, 39% utilized a basal/bolus regimen, 40% rapid-acting prandial insulin alone, 1% basal alone, 16.4% insulin pumps, and 3.8% NPH. In 2012, more CF patients were treated with steroids than in more recent years, but in many cases NPH was added to existing insulin regimens to account for steroid-induced hyperglycemia caused by the methylprednisolone used in those study participants. The authors of the study do not provide specific outcomes data regarding the various regimens used; however, they do make some inpatient treatment recommendations. They suggest using basal insulin for those with fasting hyperglycemia, and for those without fasting hyperglycemia, prandial insulin alone may be sufficient. Sometimes in early or milder cases of CFRD only correction scale could be initiated until further data demonstrates need for additional standing insulin orders. Optimal insulin dosing strategy may involve carbohydrate counting given unpredictable oral intake while inpatient, but this would be a challenging way to determine insulin doses in the hospital setting at some institutions. In the study population, 70/30 mixed insulin divided into three daily doses was used for those on tube feeds, though mixed insulin is typically not recommended for inpatient use given comparable glycemic control with increased risk of hypoglycemia when compared to basal/bolus regimens [36]. Nursing staff should be made aware of the higher risk of lipohypertrophy in slender CFRD patients and should be trained on how to properly

rotate injection sites to minimize the risk. Continuing in-patient use of insulin pumps for those able and willing to manage a pump allows for easy accommodation for acute illness hyperglycemia or steroid hyperglycemia. Insulin pumps, especially newer closed-loop systems, are helpful in reducing hyperglycemia and hypoglycemia risk. Implementation of insulin-to-carbohydrate ratio calculations for those able to count carbohydrates is also made easy by the insulin pump software.

While the 2022 update to the American Association of Clinical Endocrinology Clinical Practice Guideline for diabetes included a recommendation to consider inpatient use of DPP-IV inhibitors in non-ICU patients with T2DM and mild-to-moderate hyperglycemia [37], for reasons later discussed, this class of medication may not be appropriate for CFRD patients in or out of the hospital.

Just as with outpatient management of CFRD and with inpatient management of DM (non-CF), frequent FSBG monitoring is crucial for best outcomes. HbA1c is less reliable in patients with CFRD compared to the non-CF population, so inpatient blood glucose data can be extremely helpful in assessing a patient's glucose control. Regular inpatient use of CGM for CFRD patients is an exciting future prospect.

Non-insulin DM Agents

While insulin therapy is generally the standard for inpatient glycemic management, non-insulin agents are important to consider for transitions of care planning. The above referenced 2016 Cochrane review comparing short- versus long-acting insulin also included comparison to oral agents. No agent was found to be superior in managing CFRD [27]. A 2020 update to the Cochrane review included one newer study comparing use of insulin versus repaglinide but drew the same conclusion [38]. The International Society for Pediatric and Adolescent Diabetes clinical practice consensus guidelines and the CFF recommend treatment of CFRD with insulin and reservation of the use of oral hypoglycemia agents to clinical trials though there are CF centers that use oral agents to treat CFRD [26, 27, 39, 40].

Repaglinide

This meglitinide agent has more data on use in patients with CFRD than any other non-insulin agent though this is based primarily on two multicenter randomized trials comparing its use to insulin [21]. Meglitinides help achieve euglycemia through glucose-dependent release of insulin [41]. Ballman et al. showed no difference in HbA1c or lung function between patients randomized to either repaglinide or regular insulin therapy [4]. After 12 months of therapy, the insulin group had greater improvement in BMI, but by 24 months, neither group experienced sustained weight gain. Moran et al. compared repaglinide versus rapid acting insulin in CFRD patients; they reported improved BMI in the insulin group at 6 months and sustained

at 12 months, while the repaglinide group enjoyed only short-term BMI improvement at 6 months with reversal by 12 months. There was no significant change in HbA1c in either group [21]. Another study by Moran et al. compared peak and post-prandial glucose levels at 2 h and 5 h in 7 patients with CFRD without fasting hyperglycemia [42]. The group receiving insulin lispro had better improvement in glucose values compared to repaglinide, but neither group achieved normal blood glucose at the doses used in the study. Further research comparing dosing regimens of insulin versus repaglinide is needed [5, 42].

GLP-1 Receptor Agonists

While fasting hyperglycemia occurs later in the course of CFRD, post-prandial hyperglycemia occurs earlier. Patients with CFRD have a lack of first phase insulin release in response to a nutrient bolus, resulting in dysglycemia. This correlates with diminished incretin effect [21]. For this reason, it has been hypothesized that incretin mimetics such as GLP-1 agonists should ameliorate the effects of metabolic derangements typically seen in CFRD. These agents enhance insulin release, slow gastric emptying and reduce glucagon release, and perhaps can preserve beta cell survival [5, 21]. There is conflicting evidence as to whether or not the hormone GLP-1 is present to a lesser degree in patients with CFRD. A randomized, double-blind, cross-over trial including 32 adults with glucose-intolerant, pancreatic insufficient CF revealed that GLP-1 but not GIP increases glucose-dependent insulin secretion [43]. A small, double-blind, randomized trial showed that in young CF patients with impaired glucose tolerance, GLP-1 agonist therapy with exenatide 2.5 mcg successfully controlled post-meal hyperglycemia compared to placebo. This was thought to be more a function of slowed gastric emptying rather than increase in insulin release [44]. A clinical research article published in JCEM in 2020 described a case in which low-dose (0.13 mg then 0.16 mg) semaglutide used in conjunction with basal insulin reduced post-prandial hyperglycemia and eliminated hypoglycemia in a young man with CFRD previously on basal and bolus insulin. While he did lose 2 kg during 6 months of semaglutide treatment, he did not experience any nausea, abdominal pain, or diarrhea while using semaglutide [45]. Nevertheless, the side effects of nausea, vomiting, weight loss and increased risk for pancreatitis make the use of GLP-1 in patients with CF concerning [5, 21, 45]. It was suggested in a 2020 publication that liraglutide use in T1DM resulted in weight loss limited to adipose tissue with lean body mass spared, which would be especially important for the CFRD population [46]. Of note, pancreatic enzyme replacement therapy has been associated with improved GLP-1 production in CF patients [5].

DPP-IV Inhibitors

DPP-IV is an enzyme that inactivates metabolically active enzymes in the gut such as GLP-1 and GIP [47]. The DPP-IV inhibitors are pharmacologic agents that inhibit the enzyme DPP-IV, ultimately resulting in improved glycemic control. They have less HbA1c-lowering effect when compared to GLP-1 agonists [48]. It has been reported that DPP-IV inhibitors are associated with a lower risk of pancreatitis and weight loss [21], and for this reason, these agents may be preferred over GLP-1 agonists in the treatment of CFRD. However, a 2019 meta-analysis of 11 cardiovascular outcome trials in which 55,921 patients used GLP-1 agonists and 43,306 patients used DPP-IV inhibitors showed no significant increase in risk of acute pancreatitis from GLP-1 agonists but did show a 75% increase in risk of acute pancreatitis from DPP-IV inhibitors. The mechanism by which DPP-IV inhibitors causes pancreatitis is unclear [49]. Clinical trials demonstrating DPP-IV efficacy and safety in patients with CFRD are lacking [21].

Metformin

Metformin has not been recommended to treat CFRD historically due to concern over GI side effects and possible weight loss [21, 50]. A study of 18 CFRD patients with BMI at or above goal demonstrated metformin tolerability and no change in weight over the first 6 months [50].

Future Directions

As new CFTR modulators have come into widespread use, PwCF have experienced multifaceted clinical improvements, including increased FEV1, fewer Pexs, and improved nutritional status and quality of life measures [31]. ETI is a new CFTR modulator shown to improve pulmonary and nutritional status in CF patients. ETI use in adults with CF with or without CFRD leads to reduced hyperglycemia and improved glycemic variability as captured by CGM [31]. Advanced CF treatments are improving life expectancy and quality of life for PwCF, thus unsurprisingly, the health needs are evolving. Obesity prevalence is increasing, resulting in the need to modify and personalize dietary counseling as nutritional recommendations may differ amongst CF patients of varying phenotypes. Recommendations such as dietary changes and increasing exercise similar to those made in T2DM management may be a new focus of change for some PwCF and CFRD.

Conclusion

CFRD is associated with increased risk for Pexs and deterioration of lung function, and long-term complications. While screening measures are recommended as an outpatient procedure, all too frequent, CFRD may be newly diagnosed as an in-patient for a person hospitalized for a CF Pex. Treatment course should be followed closely during both hospitalization and post-discharge follow-up to determine the trajectory of dysglycemia and overall recovery. Importantly, the CF care should remain multidisciplinary with all involved specialists.

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Chapter 17

Inpatient Management of Diabetes During Pregnancy



Rawann Nassar, David W. Lam, and Nirali A. Shah

Introduction

In the United States, 1–2% of pregnant women have type 1 diabetes mellitus (T1DM) or type 2 diabetes mellitus (T2DM), and 6–9% of pregnant women develop gestational diabetes (GDM). There has been a 56% increase in women with GDM and a 37% increase in women with pre-existing T1DM or T2DM (also called pre-gestational DM) from 2000 to 2010 [1]. Patients with GDM can be categorized as having either GDMA1 (in which lifestyle modifications alone are sufficient to maintain glycemic targets) or GDMA2 (in whom lifestyle interventions are insufficient to maintain target and in whom pharmacotherapy is required) [2]. It is important to recognize that regardless of the type of diabetes present, all forms of diabetes are additionally characterized by an increased level of insulin resistance during pregnancy secondary to placental hormones such as human placental lactogen, placental growth hormone, prolactin, progesterone, and cortisol. Additional contributors to this insulin-resistant state are TNF alpha and leptin [3, 4].

Optimal antenatal and intrapartum glycemic management can prevent deleterious effects on both the mother and the fetus. During pregnancy, glycemic targets are much stricter than they are outside of pregnancy given the adverse outcomes that can result from suboptimal control. Elevated blood glucose in the first 6–8 weeks is associated with an increase in spontaneous abortions and congenital malformations [5]. In later weeks, the consequences of elevated maternal blood glucose result in elevated fetal insulin levels and accelerated growth which results in macrosomia. This leads to a higher chance of cesarean section delivery, shoulder dystocia, birth

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trauma, neonatal hypoglycemia, hyperbilirubinemia, polycythemia, and pathological hypertrophic cardiomyopathy. There is also an increased long-term risk of obesity and metabolic syndrome in both child and mother [6, 7].

In this chapter, we focus primarily on the *inpatient* management of diabetes during pregnancy, which is distinct from outpatient management. There are many situations in which a pregnant patient with diabetes may have to be admitted during pregnancy. Possible reasons for hospitalization include inpatient management of a non-diabetes medical illness, complications of pregnancy such as preeclampsia, pre-term labor, or premature rupture of membranes. The more frequent circumstance is an admission for labor itself, or c-section delivery, whether planned or emergent. Other scenarios include admission for glycemic control when adequate control has not been possible in the outpatient setting either due to hyperglycemia or frequent hypoglycemia. In some situations, women are admitted for the management of diabetic ketoacidosis (DKA), a particularly life-threatening complication of diabetes.

Inpatient Glycemic Targets During Pregnancy

Glycemic targets are similar for pregnant mothers whether they have pre-existing T1DM, T2DM, or GDM, but vary based on trimester. Hemoglobin A1c (HbA1c) targets are used to assess overall control; the first trimester target is <6 to 6.5% as this range seems to be associated with the lowest risk of adverse outcomes [8]. In the second and third trimesters, the lowest risk of macrosomia is seen when the HbA1c is <6% [8]. Taking all this into account, it is recommended to aim for an HbA1C of 6–6.5% and consider an even lower target (HbA1c < 6%) if able to avoid hypoglycemia [9]. It should be noted however that the HbA1C becomes a less accurate measure of glycemic control during pregnancy and its value tends to decrease as a consequence of increased red blood cell turnover [10, 11]. Moreover, the HbA1C is an average of all data points, and for that reason, it may not necessarily illustrate the presence of post-prandial hyperglycemia which is the most relevant predictor of macrosomia. For that reason, the HbA1C is helpful but cannot replace the need for self-monitored blood glucose [9]. For inpatient management, aligned with outpatient goals, fasting and pre-meal glucoses should be ≤ 95 mg/dL, 1 h post-meal ≤ 140 mg/dL and 2 h post-meal ≤ 120 mg/dL [9]. This contrasts with the traditional permissive hyperglycemia seen in the inpatient management of diabetes in non-pregnant patients. This translates to tighter glycemic control intrapartum as well as post-partum as illustrated in Table 17.1.

The definition of hypoglycemia in pregnancy varies by organization and ranges from <60 to <70 mg/dL. Though the ADA defines hypoglycemia in pregnancy as a plasma glucose less than 70 mg/dL with the recent approval of continuous glucose monitors (CGM) in pregnancy, levels as low as 63 mg/dL and above are tolerated if patients are asymptomatic [9, 16, 17]. The American College of Obstetricians and Gynecologists (ACOG) uses a lower cutoff of <60 mg/dL in pregnancy [18].

Table 17.1 A summary of glucose targets during the peripartum period

| Glucose goal (mg/dL) | Fasting | Pre-meal | 1-h post-prandial | 2-h post-prandial | References |
|--|--|----------|-------------------|-------------------|------------|
| Pre-pregnancy | ≤95 | ≤95 | ≤140 | ≤120 | [9] |
| Pregnancy | ≤95 | ≤95 | ≤140 | ≤120 | [9] |
| Intra-partum | 72–126 for extent of labor and delivery 70–110 for extent of labor and delivery | – | – | – | [12, 13] |
| Post-partum with GDM | <100 | <100 | <140 | – | [14] |
| Post-partum with Pregestational DM | ≤110 | ≤110 | – | <160 | [14] |
| Post C-section | <110 | – | ≤160 | – | [15] |
| Breastfeeding *Check glucose before breastfeeding and 1-h post-feed, with goal glucose >100 mg/dL | 70–100 | 70–100 | <150 | <150 | [14] |

Management Guidelines for the Hospitalized Pregnant Diabetes Patient

General Measures

Medical nutritional guidance continues to be an essential component to management of diabetes during pregnancy, even during hospitalization. It is important to work with a registered dietitian (RD) and/or a certified diabetes care and education specialist (CDCES) and take into consideration the patient's home-eating habits when composing a nutritional regimen. Small frequent meals are encouraged, with average carbohydrate goals of 30 g for breakfast, 45 g each at lunch and dinner. This can also incorporate 2–3 snacks scheduled about 3 h after each meal that allow for an additional 15–20 g of carbohydrate per snack [19]. Glucose monitoring should occur fasting and 1 h post-prandial if the patient is on a diet, but every 4 h if NPO [20]. Patients receiving prandial insulin would also need monitoring of pre-prandial glucose in addition to the other time points. Ensuring that meal time insulin is administered before the meal, ideally 10–15 min before eating, is also paramount in minimizing post-prandial hyperglycemia.

Oral Antidiabetic Agents

The use of oral antidiabetic agents, specifically metformin and glyburide, during pregnancy remains controversial and as such they are not first-line therapy. While individual randomized controlled trials support limited efficacy of metformin and

glyburide in reducing glucose levels for the treatment of GDM, these agents are not recommended as the first-line treatment for GDM because they are known to cross the placenta and data on long-term safety for offspring is of some concern [12, 21–23]. They remain a viable option in those who cannot receive insulin either for personal choice, needle phobia, financial barriers, or administration barriers [12]. Providers should be aware and counsel their patients that glyburide crosses the placenta and is associated with neonatal hypoglycemia [9]. Likewise, some studies on metformin during pregnancy show an association with an increase in the offspring's weight later in life in moms who were on metformin compared to those who were on insulin [24]. The recommendation for inpatient management is to discontinue oral antidiabetic medications due to the metabolic and glycemic instability during any acute illness [25].

Insulin

Insulin remains the first-line treatment recommendation during pregnancy [12, 20]. All of the currently available human insulin preparations do not cross the placenta [26–31]. Regular insulin (U-100), insulin aspart, insulin lispro, NPH insulin, and insulin detemir all have sufficient human data to demonstrate their safety during pregnancy through randomized controlled studies and have not been shown to cause adverse maternal or fetal outcomes [8, 32–35]. In many centers, these insulins are preferred for use in pregnancy. In one study by Hod et al., insulin Aspart was shown to be non-inferior to regular human insulin with respect to maternal and fetal outcomes [33]. Cohort studies have shown no increased risk of adverse fetal outcomes with the use of insulin glargine in pregnancy compared to the use of NPH insulin [36]. Insulin glargine has been widely used during pregnancy, and outcomes have shown to be similar to NPH in pregnant patients with T1DM [37]. Additionally, in the EXPECT trial which compared the use of insulin degludec to detemir as part of a basal bolus regimen in T1DM patients, degludec was non-inferior to detemir in pregnant women with T1DM [38]. Another subtle difference to consider between these basal insulins is that in comparison to glargine, NPH insulin has a peak effect making it better suited to combat dawn phenomenon (where morning elevation in cortisol can lead to elevated blood glucose levels) during pregnancy [12].

Rapid-acting insulin analogues (Aspart and Lispro) remain the preferred agents over regular insulin for prandial coverage as they have a quicker onset of action (within 10–15 min) whereas with regular insulin it is advised that the injection be administered 30 min prior to a meal.

In hospitalized pregnant patients with pre-existing T1DM or T2DM who are on an insulin regimen at home, it is important to have a good understanding of their outpatient regimen as well as the glycemic control they have had. It is typical to continue a modified and more conservative version of their regimen whether they are on four daily injections of basal-bolus or on an insulin pump to avoid

hypoglycemia. For hospitalized pregnant women who are insulin-naïve, weight-based dosing can be done in conjunction with gestational week as described below [39]:

- In the first trimester, total daily dose (TDD) can be approximated to 0.7 u/kg/day.
- In the second trimester, TDD can be approximated to 0.8 u/kg/day.
- In the third trimester, TDD can be approximated to 0.9–1 u/kg/day.

Once the TDD has been calculated, 50% TDD should be given as basal insulin and 50% as prandial/rapid-acting insulin, which should be split up into three parts to cover each of the three main meals of the day. However, if NPH insulin is used as basal insulin, it should be given in two doses, one before breakfast and one before the evening meal or at bedtime. Timing the second NPH dose for bedtime is preferred to timing it for the evening meal as we encounter a lower risk of nocturnal hypoglycemia with this schedule [19]. Alternatively, when the main concern is fasting hyperglycemia rather than postprandial hyperglycemia, the patient can be treated solely with NPH at night; this is effective because NPH peaks around early morning and therefore is effective to treat the fasting hyperglycemia [2]. It should be noted that as a consequence of this peak, NPH has a higher rate of nocturnal hypoglycemia compared with long-acting insulins like detemir and glargin [40].

It is important to keep in mind that insulin requirements vary significantly during the course of the pregnancy with projected increases during the first few weeks, a temporary decrease during weeks 9–16, followed by an increase from week 17 until week 37, and finally a decrease in the final month of pregnancy up until delivery. As a consequence of this, there is an increased risk of hypoglycemia during weeks 9–16, especially in patient with T1DM [41].

Hypoglycemia During Pregnancy

Hypoglycemia often presents with several signs and symptoms of the counter-regulatory hormonal response such as sweating, tremors, blurry vision, and palpitations and in more severe cases can cause confusion or loss of consciousness. Evidence also shows long-term detrimental cognitive effects on the fetus with recurrent episodes of maternal hypoglycemia [42]. The risk of hypoglycemia is highest in the first trimester, because of the increased insulin sensitivity during this time as well as early pregnancy symptoms of nausea and vomiting [43]. Decreased oral intake due to nausea and vomiting, which can be severe with hyperemesis gravidarum, heightens the risk of hypoglycemia. In patients with gastroparesis, pregnancy may exacerbate nausea and emesis and in some cases last throughout the pregnancy, heightening the risk of hypoglycemia [44]. Another challenge in these patients with even short periods of vomiting or decreased oral intake is an increased predisposition to ketoacidosis [45]. Medical management is aimed at symptom relief, with antiemetics and promotility agents. Consultation with an RD can advise on dietary changes to ameliorate the gastroparesis.

The following guidelines are recommended for inpatient treatment of hypoglycemia [46]:

- For glucose 60–70 mg/dL, if the patient is symptomatic and can tolerate PO, then provide 15–20 g of rapid-acting carbohydrates (equivalent is 4 oz juice or 8 oz milk) or glucose tablets/gel [46]
- For glucose \leq 60 mg/dL and the patient is alert:
 - If the patient can tolerate PO, then provide 15–20 g of rapid acting carbohydrates (equivalent is 4 oz juice or 8 oz milk) or glucose tablets/gel
 - If the patient is NPO, then provide 20–30 cc D50 IV and then start D5-normal saline at 125 cc/h. If no IV access is present, then administer glucagon 1 mg IM, after which obtain IV access and begin D5-normal saline as described above [46]
- For glucose \leq 60 mg/dL and the patient has altered mental status:
 - Notify rapid response team and escalate care as appropriate
 - Administer D50 IV (1 amp or 50 cc) and start D5-normal saline at 125 cc/h. If no IV access is present, then administer glucagon 1 mg IM, after which obtain IV access and begin D5-normal saline as described above [46]
- Fingerstick glucose should be repeated in 15 min

Intrapartum (Labor and Delivery)

The therapeutic goal during the intrapartum period is to prevent maternal hyperglycemia thereby minimizing the risk of neonatal hypoglycemia as well as fetal hypoxemia [19]. This risk persists despite optimal antenatal glycemic control in the mother [47, 48]. Approximately 50% of newborns born to mothers with diabetes will experience hypoglycemia after birth [47, 49]. Outcomes relating to the hypoglycemia event in the newborn depend on several factors including the duration and severity of hypoglycemia, the etiology, and lastly whether ICU transfer was required [47].

The ACOG recommends an intrapartum target glucose of 70–110 mg/dL [19]. However, there is some evidence that shows no associated increased risk of poor neonatal outcomes even up to a blood glucose of 140 mg/dL [13]. While mothers with T1DM mostly require insulin to prevent DKA during the high stress intrapartum phase, it is more variable in mothers with T2DM depending on their degree of relative insulin deficiency during this great physical stressor as caused by the state of insulin resistance.

Intrapartum glycemic management is dependent upon the degree of insulin sensitivity prior to pregnancy, the mode of delivery expected (vaginal versus C-section), and finally the phase of labor [15, 19, 50]. In order to discuss intrapartum glycemic management, one must divide labor into the initial latent phase of labor and the later

active phase of labor. This is important because insulin requirements vary during the different phases because of the different physiologic processes and metabolic demand.

Insulin requirements during the latent phase are typically higher compared to the active phase due to higher metabolic demand and increased glucose utilization during the active phase. During active labor, because of maternal pushing, there is an increase in glucose utilization and consequently lower insulin requirements. Following active labor, upon delivery of the placenta, there is a dramatic decrease in insulin requirements, increasing the risk of maternal hypoglycemia during this stage [51, 52].

Glycemic Monitoring and Management in Latent Phase of Labor

Glucose should be checked fasting and 1 hour post-prandial if the patient is on a diet, but once NPO, it is checked every 4 h [20]. For planned admissions, such as a scheduled induction, patients already on insulin should be instructed to administer the routine home dose of intermediate-acting or long-acting insulin the night before [50]. In the morning of induction, any intermediate-acting insulin may need to be held or the dose reduced based on most recent glycemic control [50]. Patients can then be transitioned to as needed IV insulin and IV dextrose infusions to allow for narrow glycemic targets [14, 52, 53].

Glycemic Monitoring and Management in Active Phase of Labor

Due to the NPO status of patients during active labor, bolus or continuous intravenous glucose supplementation may be needed. Patients with T1DM may need concomitant insulin treatment to avoid DKA. Intravenous insulin is recommended if glucose levels are >140 mg/dL. Patients with GDMA1 who are diet-controlled antepartum often do not require IV insulin during labor. In those with GDM, it may be possible to avoid intravenous insulin by alternating dextrose-containing solutions with non-dextrose containing solutions based on the patient's plasma glucose levels [54, 55].

Due to the narrow glycemic targets and labile insulin requirements during labor, it is preferable to switch patients on basal-bolus regimen to a continuous intravenous regular insulin infusion during the peripartum period with the option of supplemental dextrose as needed in order to tightly regulate the blood glucose levels [14, 52, 53].

ACOG recommends the following considerations to guide insulin management during active labor and delivery [50, 56–58]:

- Start a normal saline infusion in the IV.
- At the start of active labor and/or once the capillary glucose is <70 mg/dL, switch to D5W (5% dextrose) at a rate of 2.5 mL/kg/min [56, 57]
- If capillary glucose exceeds 100 mg/dL, start an insulin infusion/drip (regular insulin) at a rate of 1.25 units/h [56, 57]
- Monitor capillary glucose hourly, and adjust insulin infusion dextrose infusion rate to target a capillary glucose of 100 mg/dL. When far from target glucose, monitor glucose every 30 min rather than every hour.

There are several IV insulin protocols published in the literature [8, 14, 56], but institutions may utilize their own customized algorithms based on the above principles. One particular insulin protocol that is well cited is that of Dude et al. which provides detailed instruction on insulin drip titration [15, 52]. Once a diet is resumed, patients can then be transitioned back to subcutaneous insulin injections. For those with T1DM, the recommendation is to overlap the first dose of the basal injection with the insulin drip by approximately 2 h. For those with GDM, a sliding scale alone may work initially, while for those with T2DM, this would depend on pregestational insulin requirements. While on the insulin drip, the blood glucose should be monitored hourly in order to safely titrate the drip, and dextrose is usually initiated if the glucose drops below 120 mg/dL [8].

Glycemic Monitoring and Management in Special Scenarios

C-Section

Planned procedures such as c-section warrant important considerations to reduce the risk of hypoglycemia. Pregestational DM patients who are on long-acting insulin at home should be advised to take 50–80% of their dose prior to c-section delivery if their procedure is scheduled for early morning. The exact amount of reduction will depend on the patient's most recent fasting glycemic control. If they are on intermediate-acting insulin, they will generally take their full dose of insulin the night before. For women on an insulin pump, the equivalent of this is a 50% reduction in their basal rate which can be implemented at the start of the procedure rather than the evening before. Patients on metformin should skip the dose the morning of surgery and those taking glyburide should either reduce or omit the evening dose prior to surgery, as well as omit the dose the morning of surgery [14, 46].

When possible, c-section delivery should be scheduled as early as possible in the morning to avoid prolonged fasting and risk of hypoglycemia [59]. During the c-section procedure, serum glucose is monitored hourly and employ the measures described below [32, 46, 59]:

- If glucose is 70–110 mg/dL, can begin with non-dextrose IV fluids for hydration
- If glucose is <70 mg/dL, begin with dextrose supplementation in the IV
- If glucose is >110 mg/dL twice in a row, begin insulin drip as well as dextrose fluids
- Once target glucose is reached, stop the insulin drip, if possible, to limit dextrose fluid administration during the procedure itself
- During the procedure, continue to check capillary glucose hourly and supplement with either dextrose alone or dextrose and insulin drip depending on blood glucose
- If at the time of placental delivery, the patient is still on insulin drip, monitor glucose closely to taper off the insulin drip and avoid hypoglycemia

Insulin Pump

Patients on insulin pumps can either be transitioned to IV insulin or continue use of their insulin pumps during labor and C-section deliveries. The INSPIRED observational cohort study demonstrated that continuation of insulin pump therapy in patients with T1DM during labor and delivery was not only safe but also resulted in superior glucose control compared with those that were switched to IV insulin therapy [53]. If the patient prefers not to use their pump, is not able to self-manage during hospitalization, or if there is no endocrinology consultant available to troubleshoot pump-related issues, the patient must be transitioned to an insulin drip [14, 46].

For those in whom insulin pump is continued, besides hourly glucose measurements, there should be frequent revision of pump settings, specifically the basal rates, through the different stages of labor/procedure. Of utmost importance is the coordination between the obstetric team, nursing, endocrine consultants, and the patient to avoid adverse events such as hyper- and hypoglycemia.

Several protocols exist to guide intrapartum insulin pump dose adjustment. According to Gabbe et al., one approach is to decrease the basal rate by 30% once contractions are regular and/or the patient is on a non-caloric diet and then further to 50% during the active phase of labor and in the postpartum period (for women who required insulin prior to pregnancy) [59]. For c-section, the basal rate should be decreased by half or more starting right before the procedure [59]. In a separate study by Fresa et al., a different protocol was used as described in Table 17.2 [60].

Continuous Glucose Monitoring Systems

Continuous glucose monitoring systems (CGMs) are patient-worn devices that provide continuous estimated blood glucose measurements based on interstitial fluid glucose measurements. The sensor component sits in the interstitial fluid and detects the glucose concentration, while the transmitter, which is attached to the sensor,

Table 17.2 Intrapartum insulin management for patients on insulin pump [60]

| |
|---|
| <i>During latent labor (or long before anesthesia initiation in the case of C-section)</i> |
| <ul style="list-style-type: none"> • If blood glucose >140 mg/dL administer a correction bolus (0.5–2 U) and continue the same hourly insulin rate as their original basal rate • If blood glucose 70–140 mg/dL simply continue the same hourly insulin rate as their original basal rate • If blood glucose <70 mg/dL reduce hourly insulin rate by 50% of their prior pump basal rate (in more nuance, those who were on very high doses of insulin received a 70% reduction instead, while those who were on very low doses received a 30% reduction instead) • If blood glucose <50 mg/dL modify to an hourly rate of 0.1–0.2 u/h |
| <i>During active labor (or immediately before anesthesia initiation in the case of C-section)</i> |
| <ul style="list-style-type: none"> • If blood glucose >180 mg/dL stop the insulin pump and switch to an IV insulin protocol • If blood glucose 141–180 mg/dL simply continue the same hourly insulin rate as their original basal rate, start IV dextrose at 80 mL/h, and administer a correction bolus (0.5–2 U). For c-sections, when the blood glucose is >140 mg/dL right before anesthesia, the original hourly rate is continued for 1 h after anesthesia after which a 50% reduction was made to the hourly rate • If blood glucose 70–140 mg/dL modify to an hourly rate that is a 50% reduction from the patient's original pump basal rate (or 70% reduction if on very high doses, and 30% reduction if on very low doses) and start IV dextrose at 80–100 mL/h • If blood glucose 60–69 mg/dL modify to an hourly rate of 0.1–0.2 u/h and start IV dextrose at 80–100 mL/h • If blood glucose <60 mg/dL modify to an hourly rate of 0.1–0.2 u/h and start IV dextrose at 150–200 mL/h |
| In the case of c-sections or spontaneous labor, these rules were implemented at the time of admission whereas with induced labor they were implemented 2 h after administration of intravaginal prostaglandin |
| Blood glucose is monitored every 30 min to an hour when close to target and every 30 min when far from target [59] |

transmits the data to a receiver. The receiver device is either one specific to that CGM type, or in many cases it is the patient's mobile phone. Receivers can be programmed to alert patients to hypoglycemia, hyperglycemia, or even impending hypoglycemia in many cases based on algorithmic and predictive data. CGMs have been studied extensively in non-pregnant patients and have been shown to increase time in range [61]. Studies have shown Abbott's FreeStyle Libre CGM to be comparable in accuracy to capillary glucose testing, and the Libre 2 and Libre 3 have now been FDA approved for use during pregnancy [61]. An additional study demonstrated the accuracy of the Dexcom CGM during pregnancy as well [62]. Moreover, the CONCEPTT trial goes even further to describe improved outcomes in type 1 DM patients using CGM, specifically demonstrating that there was a decreased need for NICU admission and decreased incidence of neonatal hypoglycemia and large for gestational age (LGA) babies. These outcomes were attributed to the reduction in maternal hyperglycemia in this population [63]. Recently the Dexcom G7 has been FDA approved for pregnancy and can be employed when additional glucose data is needed for control and hypoglycemia avoidance, especially when self-monitored blood glucose has not provided enough data [13].

Inpatient Management of Patients on Regular Insulin (U-500)

U-500 is a formulation of insulin that is five times as concentrated as U-100, containing 500 units of insulin/mL rather than 100 units/mL. Due to its smaller volume, there is better absorption especially in cases where total daily dosing exceeds 200–300 units of U-100 insulin per day [15]. It also has a prolonged absorption time relative to U-100, giving it a pharmacokinetic profile more like that of NPH. Although it has a 30-min onset of action and a 2–4 h time to peak effect, unlike U-100 rapid-acting insulin, it has a 10–24 h duration of action [64].

Insulin requirements during pregnancy may triple in some cases by the third trimester [65]. There have been several case reports showing better glycemic control with U-500 in pregnancies requiring high doses of insulin, but no clinical trials have evaluated safety and efficacy in pregnancy [66, 67]. Also, due to its higher potency, U-500 carries an increased risk of hypoglycemia. For these reasons, a conversation should be held with the patient regarding the benefits, limitations, and risks of using this insulin formulation so that an informed decision can be made. Risks associated with the use of U-500 in the inpatient setting include fatal errors associated with small differences in volumetric dosing (i.e., because it is so concentrated, small increments in volume may result in large increments in insulin units) [64]. For this reason, some medical centers restrict inpatient use of U-500; hence for patients admitted prior to delivery for any reason, it would be recommended to switch to U-100 insulin and consider a 50% dose reduction as there is a higher risk of hypoglycemia due to decreased oral intake compared to home. During labor and delivery and prior to c-section, it is recommended to initiate intravenous insulin infusion with regular insulin (U-100) in these patients [46].

Diabetic Ketoacidosis

Management of DM in pregnancy is challenging, partly because of the new relatively insulin-deficient state rendered by the increased levels of counter-regulatory hormones such as human placental lactogen, cortisol, and glucagon which predispose patients to DKA [68]. This applies to both patients with pre-gestational diabetes and GDM, but it is especially important to recognize in T1DM because they are already ketosis-prone secondary to their complete insulin-deficient state. DKA in pregnant women may be more severe, develop more rapidly, and be associated with lower blood glucose readings than in non-pregnant counterparts. Clinically, it presents with nausea, vomiting, abdominal pain, change in sensorium, fruity breath, polyuria, polydipsia, tachycardia, and in severe cases hypotension, hyperventilation, and rapid breathing [46]. Fetal demise in maternal DKA has been shown to be as high as 35% [68]. For DKA diagnosis the following criteria need to be met: anion gap >10 mEq/L, serum bicarbonate <18 or arterial pH <7.3 indicating acidosis, and positive serum or urine ketones. DKA in pregnancy can have variable serum glucose measurements, sometimes presenting with euglycemic DKA [68].

A cornerstone of DKA management is identifying the trigger. Common triggers for DKA in this population include insulin non-adherence, infectious state, impaired insulin absorption from the injection site (whether an insulin pen/needle or pump), as well as pharmacologic (use of glucocorticoids or beta-mimetic tocolytic agents) [69]. Another risk factor for ketosis during pregnancy is a low carb diet, and although the ADA still recommends to prevent ketosis with a minimum daily carbohydrate intake of 175 g, some studies suggest that there is insufficient evidence as to whether the minimum carb requirement is quite as high as this [20, 70]. The concern with ketones in pregnancy stems from studies that show an association between elevated ketones and low childhood IQ, nonreactive nonstress tests, oligohydramnios, and fetal heart decelerations [71, 72]. Despite these findings, not all studies have been able to illustrate an association [73].

For the management algorithm of DKA, please refer to Table 17.3 adapted from the algorithm by Kitabchi et al. [74] Lastly, given the significant incidence of fetal demise in DKA, early recognition, trigger elimination, and timely treatment are imperative [2].

Betamethasone Treatment in Preterm Labor

In cases of preterm labor prior to 34 weeks, betamethasone is indicated for lung maturation and to reduce the risk of acute respiratory distress syndrome in the fetus. Betamethasone 12 mg is administered on day 1, and another 12 mg is administered on day 2. Consequences of steroid administration include steroid-induced hyperglycemia which further presents challenges in the management of diabetes in pregnancy [2]. A detailed algorithm for insulin titration in this scenario was described by Mathiesen et al. [75] (Table 17.4).

Table 17.3 Diabetic ketoacidosis algorithm [74]

Make diagnosis and identify triggers possible triggers include infection, cardiovascular event/stroke, surgery/trauma, non-adherence to medication, alcohol, drug use, pregnancy, pump failure

IV fluids

Initial approach

- Mild dehydration → evaluate corrected serum sodium
 - High or normal serum $[Na^+]$: start 0.45% NaCl at 250–500 mL/h
 - Low serum $[Na^+]$: start 0.9% NaCl at 250–500 mL/h
- Severe hypovolemia → start 0.9% NaCl (1 L/h) until volume restored
- Cardiogenic shock → hemodynamic monitoring ± pressors + escalation of care

Once blood glucose ≤ 200 mg/dL transition to D5-½ normal saline at 150–250 mL/h

Hydration target is to attain appropriate urine output of approximately 50 mL/h

Insulin

Initial approach

- IV insulin pathway (used for more serious DKA presentation)
 - Administer regular IV insulin 0.1 u/kg as an IV bolus
 - Subsequently, start 0.1 u/kg/h IV continuous insulin infusion
- Subcutaneous insulin pathway (used for uncomplicated DKA):
 - Administer rapid acting subQ insulin 0.3 u/kg then 1 h later administer 0.2 u/kg
 - Subsequently start 0.2 u/kg subcutaneously every 2 h

If serum glucose does not decrease by 50–70 mg/dL in the first hour, then double the IV infusion rate or the subcutaneous insulin bolus depending on which pathway has been employed

Once blood glucose ≤ 200 mg/dL reduce regular insulin drip rate to 0.05–0.1 u/kg/h (if on IV insulin pathway) or decrease rapid -acting insulin bolus to 0.1 u/kg every 2 h (if on subcutaneous insulin pathway)

Maintain blood glucose 150–200 mg/dL until DKA has resolved

Potassium

- If serum $K^+ < 3.3$ mEq/L, hold insulin and replete with 20–30 mEq K per hour until level > 3.3
- If serum $K^+ > 3.3$ but < 5.3 mEq/L, replete with 20–30 mEq K per liter of IV fluid to keep level between 4 and 5 mEq/L
- If serum $K^+ \geq 5.3$ mEq/L, simply continue to monitor level every 2 h to ensure remains normal

Bicarbonate

Initial approach

- pH < 6.9 → dilute 100 mmol sodium bicarbonate in 400 mL H_2O with 20 mEq KCl and infuse for 2 h
- pH 6.9–7.0 → dilute 50 mmol sodium bicarbonate in 200 mL H_2O with 10 mEq KCl and infuse for 1 h
- pH > 7.0 → no sodium bicarbonate indicated here

As long as pH < 7.0 , can repeat sodium bicarbonate administration every 2 h

Continue to monitor serum $[K^+]$ as mentioned above as level can fluctuate with acid-base change

Lab monitoring

(continued)

Table 17.3 (continued)

- Monitor the following labs every 2–4 h until stable BUN, venous pH, creatinine, glucose, electrolytes (namely Na, K, Mag, P)

Next steps after resolution of DKA

- Once DKA has resolved and if patient is able to tolerate PO, transition to subcutaneous basal-bolus insulin regimen
- It is critical to bridge long-acting insulin with continuous IV insulin for 1–2 h to allow for long-acting insulin to equilibrate in plasma, thus preventing re-emergence of DKA
- Recommended regimen in insulin-naïve patient is 0.5–0.8 u/kg of TDD, split up into basal and bolus doses

Table 17.4 Insulin adjustment algorithm for betamethasone steroid hyperglycemia [75]

| Day since first betamethasone dose | Insulin adjustment |
|------------------------------------|--|
| Day 1 (day of first dose) | Increase PM insulin dose by 25% compared to baseline dose |
| Day 2 | Increase all insulin doses by 45% compared to baseline dose |
| Day 3 | Increase all insulin doses by 40% compared to baseline dose |
| Day 4 | Increase all insulin doses by 30% compared to baseline dose |
| Day 5 | Increase all insulin doses by 10% compared to baseline dose |
| Days 6 and 7 | Reduce insulin doses back down to baseline * Note that by now the pregnancy has progressed by 7 days and therefore insulin requirements are likely higher now |

Conclusion

The inpatient management of diabetes during pregnancy can be challenging due to many of the factors discussed. The impact of not achieving stringent glucose levels renders both mother and neonate at much higher risk of significant detrimental sequelae in the immediate future but also long-term. However, inpatient glycemic control is attainable with initiation of insulin therapy and adherence to protocols, attentive care and monitoring, and effective team communication.

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Chapter 18

Postpartum Diabetes Management



Nancy Drobyski and Jessica Abramowitz

Introduction

According to the Centers for Disease Control and Prevention (CDC), more than 37 million Americans or 11.3% of the US population have diabetes mellitus (DM), with more than eight million of these persons being unaware of their diagnosis [1]. Approximately 1.4 million new cases of DM were diagnosed in 2019, including an estimated 675,000 women, with an estimated 401,000 of these women between the reproductive age of 18 and 44 years [1]. An additional 96 million Americans over the age of 18 years have pre-diabetes, representing 38% of the US population [1]. As a direct result of the overall increase in diagnosis of diabetes, pre-diabetes, and the obesity epidemic, there is a consequential increase in the number of women with pre-existing diabetes in pregnancy and gestational diabetes mellitus (GDM) [2].

GDM is defined as glucose intolerance that first occurs during pregnancy, regardless of the degree of hyperglycemia [3]. In GDM glucose levels tend to normalize after the delivery of the placenta, though there may be unrecognized beta cell dysfunction which could lead to the development of type 2 diabetes (T2DM) later in life [3]. The prevalence of GDM has increased on both a national and global level. In 2020, the national rate of GDM was 7.8 per 100 births and represents an increase of 30% from 2016 [4]. The average annual percent change for the years 2016–2019 was 3%, but between 2019 and 2020, there was an increase of 9% [4].

Both pre-existing diabetes in pregnancy (also called pre-gestational DM and inclusive of type 1 DM [T1DM] and T2DM) and GDM place women and their offspring at significant risk for adverse outcomes including (but not limited to)

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spontaneous abortion, preeclampsia, fetal anomalies, fetal demise, macrosomia, neonatal hypoglycemia, neonatal respiratory distress syndrome, and neonatal jaundice [2, 4].

In addition to the above adverse outcomes, there is a consequential risk of maternal death. Of note, maternal death is considered to be a significant indicator of the health of a nation or state. It is defined as the death of a woman during pregnancy or within 42 days of the end of the pregnancy [5]. Maternal morbidity and mortality rates for American women increased significantly from 7.2 deaths per 100,000 births in 1987 to 18 deaths per 100,000 births in 2018. When compared with white women, women of color had a much higher rate at 40 deaths per 100,000 live births versus 12.4 deaths per 100,000 live births for white women. Comorbidities accounting for this increase include obesity, diabetes, cardiovascular disease, and hypertension, which in turn have increased the rate of cesarean birth and poor wound healing [6].

After delivering her offspring, the new mother is challenged with recovering from delivery, dealing with her fluctuating hormone levels, and learning to care for her new infant in addition to the endless self-care demands of diabetes mellitus. These additional responsibilities are best handled with the support of others including the maternal family unit and the healthcare team.

This chapter will focus on the postpartum care and management of women with diabetes and its associated comorbidities. When compared with available literature and guidelines on the care of the woman with DM during pregnancy, there is a paucity of literature and guidelines focusing on diabetes care and management in the postpartum period. Topics to be covered include postpartum physiology, glucose monitoring, medication management, insulin management, lifestyle interventions, lactation, postpartum screening, and care delivery between pregnancies.

Postpartum Physiology

Hormonal changes occur throughout pregnancy that affect insulin requirements, and there is a change in the endocrine milieu and insulin requirements in the postpartum period. The state of insulin resistance that occurs during pregnancy is mediated by placental hormone production including growth factors and cytokines [7].

During active labor there is an initial decrease in insulin requirements likely related to increased insulin utilization as well as an increase in insulin clearance [8]. This is followed by further decreases in insulin requirements, by roughly 34%, following delivery of the placenta [2, 7, 9]. Insulin sensitivity generally returns to pre-pregnancy levels over the next 1–2 weeks [2]. For women with type 1 diabetes, insulin requirements typically decrease to pre-pregnancy levels or may be lower, and there can be a period of time with very low to no insulin requirement at all [8]. This lack of insulin requirement is likely due to the loss of insulin resistance mediated by the hormones of pregnancy, along with erratic maternal eating and sleep schedules [2]. One retrospective chart review of women with type 1 diabetes with

singleton pregnancies over a 5-year period found that the duration of insulin independence was inversely related to the time from last dose of long-acting or intermediate-acting insulin and continuation of the insulin infusion. There were 2 women of the 36 with no insulin requirements for 24 h. There was no correlation between mode of delivery and duration of insulin independence [8]. Insulin requirements for women with type 1 diabetes may also not reach pre-pregnancy levels in the setting of lactation [10].

Vital birth data from the CDC for 2020 found that approximately 30% of all deliveries in the United States were via cesarean section [11]. Obesity and diabetes are both known risk factors for surgical delivery [12]. Glycemic control in the postpartum period is important for prevention of wound infection and to promote healing [13]. For women with type 2 diabetes, insulin requirements may be variable in the postpartum period; and based on the glucose levels, insulin may be discontinued, or the dose can be decreased [14]. In women with GDM, glucose levels can be monitored in the postpartum period to best determine their insulin or medication requirement [14]. There is evidence that some cases of GDM do represent pre-existing diabetes, as there is minimal routine screening performed for diabetes in non-pregnant individuals of reproductive age [3]. This can represent a diagnostic and treatment dilemma upon hospital discharge and typically requires close follow-up and postpartum monitoring.

It has been noted that breastfeeding in the early postpartum period not only has benefits for the newborn but also for the mother and has been shown to improve glycemic control in the short term as well as prevent type 2 diabetes in the longer term [15]. A systematic review of studies examining lactation and glycemic control found that breastfeeding both reduced the fasting plasma glucose level as well as risk of impaired fasting glucose [16].

Glucose Monitoring

Frequency, Mode, and Glycemic Targets

Guidelines recommend a glucose target of 72–126 mg/dL during labor and delivery [17]. For women with type 1 and type 2 diabetes, glucose levels should be monitored in the postpartum period before meals and bedtime, and an overnight glucose check may be considered in the setting of potential overnight hypoglycemia. For individuals not immediately started on a meal plan, glucose levels can be monitored every 4–6 hours. The standard of care for glucose monitoring in the inpatient setting is via point of care (POC) capillary glucose testing. There are more patients using continuous glucose monitoring (CGM) in the outpatient setting both during and prior to pregnancy. CGM allows for the measurement of interstitial glucose every 5 min and allows for more intensive glucose monitoring over a 24-h period. CGM use with confirmatory POC glucose is recommended in the inpatient setting for

adults with diabetes who are treated with insulin and are at high risk for hypoglycemia [18]. CGM may also be used in conjunction with hybrid closed loop insulin pumps in the inpatient setting as well [18]. There are specific clinical conditions in which CGM use may not be accurate including extensive skin infection, hypoperfusion, hypovolemia, or those on vasopressor therapy [18].

Glycemic targets for non-critically ill patients should be utilized for women postpartum with glucose levels of 100–180 mg/dL or a less stringent target of 140–180 mg/dL if patients are critically ill [18, 19]. After hospital discharge, patients on basal-bolus insulin should continue this glucose monitoring schedule if using POC testing at home or they may continue CGM use.

For women with a diagnosis of GDM, it is recommended that glucose-lowering medications be discontinued postpartum and glucose levels be checked fasting for the first 24–72 hours postpartum to assess for persistent hyperglycemia [17]. There is a need to clarify glycemic status postpartum to determine a diagnosis of GDM versus overt diabetes and enable appropriate treatment prior to future pregnancies, though this distinction is not always clear immediately.

The postpartum need for insulin is variable among women with GDM. It is recommended that a 75 g oral glucose tolerance test (OGTT) be performed at 4–12 weeks postpartum [20]. The oral glucose tolerance test is the preferred method for screening for ongoing diabetes during this time. Due to the rapid red blood cell turnover of pregnancy, possible anemia, and potential need for blood transfusion, the hemoglobin A1c level is not considered a standard measure of glucose control in pregnancy and the immediate postpartum period [2]. In addition successful postpartum screening has been best linked to attendance at the initial postpartum gynecology visit. For women who undergo testing, the incidence of impaired fasting glucose is 3–6%, while overt DM can be found in 5–14% of women who had GDM [21]. Women with GDM have an increased lifetime risk of development of diabetes between 50 and 60% [2].

Lifestyle Modification

The postpartum hospitalization period is an opportunity for patient education and further engagement in healthcare. All persons with diabetes are encouraged to engage in healthy lifestyle behaviors as part of their diabetes self-management plan. The Association of Diabetes Care and Education Specialists (ADCES) identifies seven recommended behaviors, “The ADCES 7 Self-Care Behaviors,” identified as healthy eating, being active, monitoring, taking medication, healthy coping, reducing risk, and problem-solving [22].

The American Diabetes Association (ADA) notes that women with GDM have a tenfold risk of developing T2DM when compared to women without GDM, and the risk increases linearly with each decade of life. Intensive lifestyle modification and metformin are noted to prevent and delay the onset of T2DM [23].

This section will describe the recommended postpartum lifestyle modifications for both pre-gestational DM and women with a history of GDM. It will also focus on the benefits of lactation for both mother and offspring.

Healthy Eating

The ADA acknowledges there is no one-size-fits-all meal plan for persons with diabetes, including women with pre-gestational DM and GDM. There are a plethora of factors such as cultural habits, existing comorbidities, personal preferences, competing life responsibilities, and many others that impact eating patterns and food choices. It is recommended to place the patient at the center of her care and empower her to make healthy meal plan choices that best fit her needs [24].

Postpartum Nutrition Considerations

In general, women of childbearing capacity (20–44 years of age) have been found to be nutritionally deficient in their intake of several vitamins and minerals, and 50% are overweight or obese [25].

The US Department of Agriculture and US Department of Health and Human Services publish dietary guidelines for Americans across the lifespan. The 2020 Dietary Guidelines Advisory Committee recommends the following strategies to optimize the health and nutritional status of women of childbearing capacity:

- Encourage women to achieve a healthy weight before pregnancy and aim for gestational weight gain within recommendations.
- Encourage a diet pattern high in vegetables, fruits, whole grains, nuts, legumes, seafood, and vegetable oil and low in added sugar, refined grains, and red and processed meats.
- Encourage foods and beverages that are good sources of the following shortfall nutrients: iron, folate, calcium, choline, magnesium, protein, fiber.
- Do not avoid allergenic foods (eggs, shellfish, peanuts, tree nuts, soy) during pregnancy.

These general guidelines can serve as a framework for customized meal planning, as they emphasize overall healthy eating within the context of the individual's nutritional needs and desires [26].

Non-lactating women require no additional calories but should be encouraged to employ healthy eating habits to reduce any excessive gestational weight gain and establish/maintain individualized glycemic targets. Optimizing weight between pregnancies minimizes the development of obesity and its many negative health consequences [27, 28].

The nutritional needs of the lactating woman differ from that of the non-lactating woman. According to the CDC, the caloric needs during lactation can increase by

Table 18.1 Daily nutritional needs of lactating/breastfeeding women

| Energy (kcal) | Protein | Carbohydrate | Lipid | Water |
|---|---|--|--|-----------|
| No less than 1800 kcal/day | Minimum 71 g protein (1.1 g protein/kg of pre-pregnancy weight) | Recommended Daily Allowance (RDA) 210 g/day ^a | No daily recommended intake ^b | |
| +330 kcal/day during the first 6 months of lactation (2130 kcal/day) | | | 13 g omega 6 fatty acids and 1.3 g Omega 3 fatty acids | |
| +400 kcal/day during the second 6 months of lactation (2200 kcal/day) | | | Avoid trans fats | |
| | | | | 3.8 L/day |

^a Women with pre-diabetes, type 1 and type 2 diabetes should monitor their glucose and communicate with providers for any medication adjustments and ask for medical nutrition therapy (MNT) referral for nutrition recommendations. Adjustments based on glucose control and energy expenditure (physical activity). Macronutrient requirements will vary by individual and may need to be adjusted accordingly

^b Dependent on maternal energy requirements. The Daily Recommended Intake Calculator for Healthcare Professionals, available at nal.usda.gov/fnic/dri-calculator, can be used to estimate calorie needs based on age, sex, height, weight, activity level, and pregnancy or lactation status [29]

330–400 kcal/day above pre-pregnant requirements for well-nourished breastfeeding mothers (see Table 18.1) [30], but emphasis should be placed on consumption of high-quality, nutrient-dense foods.

The eating habits of lactating women impact both the volume and nutrient composition of breast milk. This has a direct impact on the growth and development of the infant.

Hypoglycemia during breastfeeding often occurs in women taking insulin. Small meals before breastfeeding may reduce the risk of hypoglycemia during lactation [31]. Insulin dose adjustments may also be needed and will be discussed in the section on medication.

Many persons with diabetes and pre-diabetes benefit from diabetes self-management education (DSME) and medical nutrition therapy (MNT). Consideration should be given to consulting the inpatient registered dietitian and diabetes care and education specialist (DCES) for MNT and DSME, as well as formally referring the patient for outpatient DSME and MNT to access individualized services for education reinforcement and follow-up [24].

Being Active

In addition to healthy eating, regular physical activity is recommended as part of an effective diabetes self-management treatment plan. It has a positive impact on the management of excessive gestational weight gain, postpartum depression, hypertension, glucose control, and many other maternal health outcomes [27]. Resuming exercise or adding a new exercise regimen is encouraged if it is medically safe. Regular physical activity may be resumed gradually based upon the method of delivery (vaginal or cesarean delivery) and the absence of medical or surgical complications [32].

For women taking insulin or insulin secretagogues, the timing of physical activity in relation to insulin administration, medication peak activity, and food intake should be considered to avoid exercise-induced hypoglycemia. Persons with diabetes have varied glycemic responses to physical activity and should be encouraged to test their glucose before, during, and after physical activity. Delayed hypoglycemia can also occur, depending on the duration and intensity of exercise, and patients should be educated on ways to prevent and manage hypoglycemia [33].

Healthy Coping

In general, up to 10% of women will experience postpartum depression within the first year after delivery [34], and depression impacts one in four persons with diabetes [33]. Women with GDM and pre-existing diabetes in pregnancy are at substantial risk for developing postpartum depression and should be screened and supported [23, 33, 35]. In addition, women with diabetes are at increased risk of an adverse pregnancy outcome, such as fetal demise [36]. This puts them at higher risk for depression and other mental health disorders [37].

Psychosocial assessment and intervention should be included as part of the patient-centered approach to diabetes care for all persons with DM. In addition to postpartum depression screening, follow-up may include assessment for anxiety, eating disorders, diabetes distress, the individual's expectations related to diabetes care and outcomes, available mental health resources, and mental health history. Assessments should be conducted at key times including at the time of hospitalization. Appropriate referrals to mental health experts for counseling and intervention should occur promptly [35].

Lactation Support

Despite the American Academy of Pediatrics' and World Health Organization's recommendation for exclusive breastfeeding in the first hour of life and for the next 6 months of life, breastfeeding rates vary among countries around the globe [38].

Some studies have demonstrated that women with T1DM are less likely to breastfeed their children and breastfeed for a shorter duration of time than women without T1DM. Reasons highlighted include increased rate of Cesarean section, pre-term delivery requiring neonatal intensive care intervention, younger maternal age, and shorter duration of education [39]. There may also be a delay in lactogenesis by up to 1 day if glycemic control has been suboptimal in pregnancy [40].

Women with pre-existing type 2 diabetes and GDM may also experience a delay in lactogenesis. Insulin use, maternal obesity, advanced maternal age, and suboptimal initiation of breastfeeding are all independent causative factors in delayed lactogenesis [38].

Women with diabetes should be strongly encouraged and supported to breastfeed. Healthcare providers should recognize that the informed decision to breastfeed and the frequency/duration of breastfeeding are always a personal decision made by the mother. Numerous benefits of breastfeeding for both mother and infant are well-supported in the literature [8, 16, 23, 38, 41].

Benefits of Breastfeeding

The American College of Obstetricians and Gynecologists (ACOG) clearly indicates that enabling women to meet their breastfeeding goals is a public health priority, and there are many evidence-based reasons for this recommendation [41]. Some risk modifications and benefits are dependent on exclusive versus partial breastfeeding and the duration/frequency of breastfeeding. It is also noted that the longer

Table 18.2 Maternal benefits of breastfeeding [41, 42]

| | |
|------------------------|---|
| Short-term benefits | <ul style="list-style-type: none"> • A reduced risk of postpartum hemorrhage • A reduction in insulin demand and insulin dose • An enhancement of maternal-child and family bonding • A prolonged absence of menses (for those exclusively breastfeeding in the first 6 months postpartum) • Decreased depression symptoms at 2, 6, and 12 months postpartum in those women reaching their breastfeeding goals |
| Long-term benefits | <ul style="list-style-type: none"> • A reduced risk of metabolic syndrome and type 2 diabetes mellitus in women with GDM • A reduced risk of cardiovascular disease, especially hypertension • A reduced risk of cancer of the breast, ovaries, thyroid, and endometrium • A more rapid return to pre-pregnancy body weight |
| Environmental benefits | <ul style="list-style-type: none"> • A reduction in the carbon footprint. (One analysis indicated that 6 months of exclusive breastfeeding saves 95–153 kg of carbon dioxide when compared with artificial feeding) |

Table 18.3 Offspring benefits of breastfeeding [40–42]

| | |
|---------------------|--|
| Short-term benefits | <p>In infants, a reduced risk of:</p> <ul style="list-style-type: none"> • Otitis media • Gastroenteritis • Respiratory tract infections • Sudden infant death syndrome <p>In preterm infants:</p> <ul style="list-style-type: none"> • A reduced risk of necrotizing enterocolitis • Higher neurodevelopment scores as toddlers |
| Long-term benefits | <p>A reduced risk of:</p> <ul style="list-style-type: none"> • Inflammatory bowel disease • Obesity • Diabetes mellitus • Asthma • Childhood leukemia |

duration and frequency of breastfeeding corresponds with greater long-term health benefits [42]. See Tables 18.2 and 18.3.

Contraception During Lactation

As noted throughout this chapter, a major barrier to preconception care is the lack of pregnancy planning. Interpregnancy duration of greater than 18 months is noted to improve outcomes in the following pregnancy [41, 42]. Providers should discuss future planning of pregnancies in the immediate postpartum period so that women can make an informed decision about which contraceptive method may work best for them.

Medication Prescription in the Postpartum Period

In the postpartum period, there is a decrease in insulin requirements for women with T1DM and T2DM, and pre-pregnancy glycemic targets can be utilized [23]. Patients with GDM that has resolved revert to normoglycemia and no longer require glucose-lowering therapy. Figure 18.1 summarizes an approach to inpatient management of postpartum diabetes. Insulin dose adjustment may require a change in the total daily dose of basal-bolus insulin injections or adjustment of insulin pump settings. Many patients may be utilizing hybrid closed loop insulin systems. These systems integrate CGM technology into the insulin pump algorithm. In the event that CGM use is not possible, the insulin pump can be used in “manual mode,” and POC capillary glucose testing may be utilized for glucose monitoring. Women with T1DM will always be discharged on an insulin-based regimen either with basal and bolus insulins or insulin pump, but with lower than usual doses postpartum and caution for hypoglycemia should be employed.

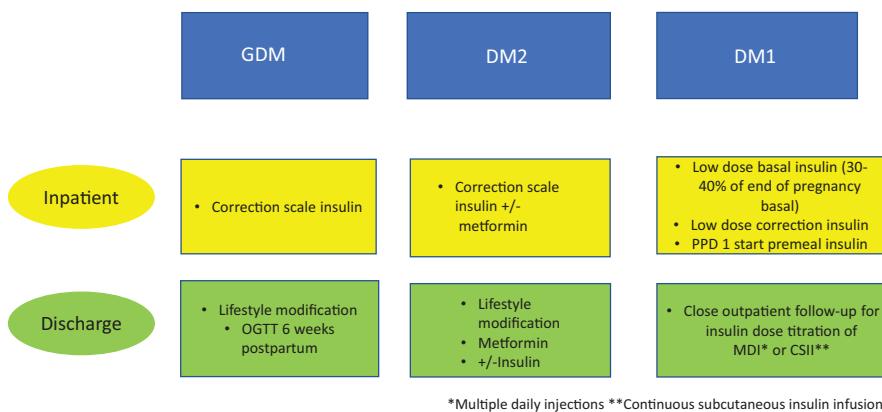


Fig. 18.1 Approach to inpatient management of postpartum diabetes. *GDM* gestational diabetes, *DM2* type 2 diabetes, *DM1* type 1 diabetes, *OGTT* oral glucose tolerance test, *PPD* postpartum day. * Multiple daily injections refers to basal and bolus insulin. ** Continuous subcutaneous insulin infusion refers to insulin pump therapy

Women with type 2 diabetes should have glucose levels checked before each meal and bedtime post-delivery. Frequently women with type 2 diabetes who may have required insulin during pregnancy will not require insulin in the postpartum period. Some women with type 2 diabetes may require basal insulin to treat fasting hyperglycemia, while few may require basal-bolus insulin to cover post prandial hyperglycemia as well [14]. Typically, insulin is preferred for management of inpatient diabetes [17]. Lactation is associated with improvement in glucose tolerance, and in women with diabetes, there can be a decrease in insulin requirement which is likely due to glucose utilization in milk production [43]. Studies have shown variable results regarding the decrease in insulin requirement [40].

At the time of hospital discharge, medication reconciliation is required, and decisions regarding diabetes medication management must be made in collaboration with the patient. When planning for discharge on insulin, the choice should be based on the best insulin for glucose management and affordability of insulin products. Due to the high cost of insulin and price caps only applying to Medicare clients, many patients may not fill insulin prescriptions or take insulin as prescribed [44].

Insulin may be prescribed for continued use outpatient, but oral medications may be considered as well. There are several oral DM medications which are known to be safe during breastfeeding. The LactMed database is an evidence-based resource that can be used to check the safety of medication use in breastfeeding, including drug levels in breast milk and serum levels in the infant. The LactMed database is available online from the National Library of Medicine. When prescribing oral or non-insulin injectable agents, an additional consideration is affordability, potential benefit, and patient choice.

Metformin, an oral biguanide medication, is typically a preferred agent for T2DM, especially in lactating mothers [43]. Metformin acts by stimulating glucose

uptake in the liver as well as in peripheral tissues and decreases hepatic glucose production and output [45]. Several studies have shown very low levels of metformin in breast milk [45–47]. Metformin can be initiated postpartum while inpatient, once tolerating oral intake, for most patients with pre-existing T2DM. Monitoring the patient on metformin between delivery and discharge may allow time for monitoring of glucose and decision regarding need for additional therapy such as insulin to be added at discharge. Taking a thorough medical history is helpful including medication used prior to pregnancy. Most women with T2DM on metformin prior to pregnancy, but then requiring insulin during pregnancy, can resume metformin monotherapy after delivery. Outpatient follow-up is important to reassess therapeutic decisions made at the time of discharge.

Sulfonylureas, a class of oral diabetes medications that stimulate beta cell insulin production, may be considered. Sulfonylureas have an associated risk of hypoglycemia, and close monitoring of glucose levels is recommended if they are prescribed. Glyburide and glipizide levels were found to be undetectable in breast milk [43].

Thiazolidinediones act to increase insulin sensitivity via action on the adipose and muscle tissues. Pioglitazone drug labeling recommends caution when used in the setting of breastfeeding. It is likely safe and excreted in only small amounts in breast milk [43].

Other medication classes that may be considered may include Dipeptidyl Peptidase-4 (DPP-4) inhibitors and Glucagon Like Peptide 1 receptor agonists (GLP-1RA). There is no information regarding DPP-4 inhibitors and excretion in breast milk, but label recommendations advise caution for use in lactating women [43]. Saxagliptin which has a shorter half-life and linagliptin, which is primarily maternal protein-bound, may be the best choices in this class [43]. GLP-1RA are administered as a subcutaneous injection either daily or weekly. There is no data regarding this class of medication and its safe use in breastfeeding.

Sodium glucose co-transporter 2 (SGLT2) inhibitors cause glucose excretion in the urine. Several of the medications in this class have high percentages of maternal protein-binding and may not be present in breast milk in large quantities [38]. Metformin is the most commonly prescribed oral diabetes medication for women with type 2 diabetes in the postpartum period given its known safety profile. For women with higher glucose levels, basal insulin may be prescribed in addition to metformin with precautions for monitoring for hypoglycemia.

In summary, in regard to choice of postpartum pharmacotherapy, metformin is well tolerated and has a known safety profile in lactation. Metformin is most commonly prescribed for women with type 2 diabetes in the postpartum period. Starting metformin postpartum while inpatient allows the provider to gauge if metformin monotherapy may be acceptable for discharge. For women with higher insulin requirements, basal insulin can be added on to metformin to optimize glycemic control, though in the case of very high requirements, prandial insulin may be needed as well. GLP-1RA may be considered once lactation is complete to assist with glycemic control as well as optimizing weight/obesity management.

Conclusion

The inpatient management of postpartum diabetes requires careful attention and consideration of the individual needs and concerns of women with diabetes. A collaborative team-based approach including the obstetrical care team, nursing team, diabetes care and education specialist, inpatient endocrinology service, and other ancillary staff are recommended for safe inpatient care and subsequent transition to outpatient care. Specific consideration should be made for diabetes self-management education and support in the hospital and upon discharge.

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Chapter 19

Perioperative Management of Blood Glucose in Adults with Diabetes Mellitus



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Introduction

Patients with DM have an increased risk of cardiovascular disease, peripheral artery disease, and microvascular complications, which often require surgical intervention in addition to requiring other types of surgeries. One important aspect of perioperative management is glycemic control; hyperglycemia has been shown to increase length of stay, morbidity and mortality, and overall postoperative adverse outcomes. This chapter will review the pathophysiology of hyperglycemia in the perioperative period, as well as discuss management of glucose in the preoperative, intraoperative, and postoperative time periods.

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Pathophysiology of Hyperglycemia and Surgery

Surgery and general anesthesia cause a neuroendocrine stress response resulting in the release of counterregulatory hormones including catecholamines, cortisol, glucagon, growth hormone, and inflammatory cytokines (e.g., interleukin-6, tumor necrosis factor-alpha) [1]. Cortisol increases hepatic gluconeogenesis and stimulates protein catabolism. Catecholamines increase glucagon secretion and inhibit insulin release by pancreatic beta cells [2]. These counterregulatory hormones lead to enhanced lipolysis and increased production of free fatty acids, which subsequently inhibit insulin-stimulated glucose uptake in skeletal muscle, causing insulin resistance [1]. Hyperglycemia results from an increased endogenous glucose production combined with a relative state of insulin resistance. The magnitude of the counterregulatory response varies per individual and is influenced by the type of anesthesia (general anesthesia > epidural) and the extent of the surgery (open > laparoscopic) [1]. Other important factors such as the anatomic location, invasiveness of the procedure, intraoperative fluids, and the use of glucocorticoid can all influence glucose control.

Overall, perioperative hyperglycemia causes delayed collagen synthesis, exaggerated inflammatory response, impaired phagocytosis, and microvascular dysfunction [3]. These effects can lead to impaired wound healing, increased rate of infections, prolonged postoperative length of stay, and increased morbidity and mortality [3, 4].

Preoperative, Intraoperative, and Postoperative Hyperglycemia

Preoperative hyperglycemia may be associated with increased length of stay (LOS), postoperative complication rates including infections, renal dysfunction, morbidity, and mortality [4, 5]. A prospective, observational study of 7565 patients concluded that both the presence of pre-existing DM and higher hemoglobin A1c (HbA1c) are independently associated with adverse outcomes after surgery including LOS, worsening renal function, intensive care unit admission, and overall morbidity and mortality [6]. Preoperative hyperglycemia has also been linked to an increased risk of pulmonary embolism after major orthopedic surgery [7]. A retrospective study of non-cardiac surgeries suggested that preoperative HbA1c greater than 8% may be associated with longer hospital LOS [8]. In a prospective study of coronary artery bypass grafting, higher HbA1c was associated with an increased incidence of death, myocardial infarction, and deep sternal wound infection [9].

Intraoperative glycemic control also affects surgical outcomes. In a prospective study of diabetes patients undergoing cardiac surgery, poor intraoperative glycemic control was associated with severe postoperative morbidity [10]. A retrospective study of cardiac surgery found that those meeting a primary endpoint (composite of

mortality, sternal infections, prolonged ventilation, cardiac arrhythmias, stroke, and renal failure) within 30 days after surgery had higher initial, mean, and maximal intraoperative glucose [11].

Postoperative hyperglycemia has been shown to be associated with increased rates of postoperative complications. In a retrospective analysis of DM patients (mean preoperative HbA1c 7.9%) who had undergone non-cardiac surgeries, higher rates of postoperative infection were associated with elevated 24-h postoperative blood glucose (BG) [12]. In another retrospective review of total joint arthroplasty, patients with a mean postoperative glucose of >200 mg/dL were at risk for increased wound complications [13].

Glucose Management Goals Based on Current Literature

HbA1c Target

HbA1c level is commonly used to determine if a patient should proceed with elective surgery [14]. Societal guidelines recommend varying HbA1c thresholds for delaying elective surgery, summarized in Table 19.1.

Currently, there is insufficient data to achieve a consensus on a specific HbA1c target above which elective ambulatory surgery should be postponed [20]. The above HbA1C recommendations apply only to patients who are scheduled for elective procedures and would have reasonable time to allow interventions to lower preoperative HbA1c. When this is not feasible, the suggested approach is to target preoperative glucose level < 180 mg/dL [15]. Fructosamine, an alternative measure of glycemic control, is a serum protein formed by spontaneous nonenzymatic glycation, which is elevated in hyperglycemia. Recent studies in patients undergoing total joint arthroplasty demonstrated that elevated preoperative fructosamine is an independent risk factor for postsurgical infection, readmission, and reoperation [21]. Future research targeting the use of continuous glucose monitoring (CGM) for perioperative optimization of glycemic control would be beneficial.

Table 19.1 Society guidelines and HbA1c thresholds for delaying elective surgery

| Society guidelines | HbA1c level for postpone surgery |
|---|--|
| American Diabetes Association (ADA) | No specific level, but recommends <8% for elective surgery |
| The Endocrine Society | >8% [15] |
| The Association of Anaesthetists of Great Britain and Ireland (AAGBI) | >8.5% [16] |
| The Joint British Societies | >8.5% refer to a specialist. Delay of surgery is individualized [17] |
| The Australian Diabetes Association | >9% [18] |
| The French Society of Anesthesia and Intensive Care Medicine | >9% [19] |

Glucose Target

Various organizations have recommended different perioperative targets to best optimize outcomes. Evidence remains insufficient to support specific BG targets at which cancellation or postponement of surgery should be considered [4, 22]. The ADA recommends perioperative BG levels of 100–180 mg/dL [23]. The Endocrine Society suggests targeting a BG of 100–180 mg/dL [15]. AACE recommends BG of 140–180 mg/dL for inpatient setting. The Society of Ambulatory Anesthesia (SAMBA) recommends that surgery be postponed when there are significant complications of hyperglycemia such as severe dehydration, diabetic ketoacidosis, or hyperosmolar nonketotic states [20]. Some experts suggest that in the absence of such complications, hyperglycemia may be treated with insulin infusion or subcutaneous insulin to achieve BG levels less than 300 mg/dL [24]. If BG levels decrease to expected levels, then surgery can proceed with the continuation of insulin therapy [24]. If hyperglycemia persists, then surgery should be postponed.

SAMBA recommends intraoperative BG levels less than 180 mg/dL [20]. Attention should be given to avoid hypoglycemia during anesthesia and in the intraoperative period. Hypoglycemia can cause life-threatening complications such as cardiac arrhythmias, seizures, functional brain failure, and even brain death [25]. In a sedated patient, symptoms and signs of hypoglycemia will be difficult, if not impossible, to detect. Therapy for hypoglycemia should be initiated when the BG level drops <70 mg/dL [20].

In a patient who is awake with hypoglycemia, the preferred method for treating hypoglycemia is the consumption of 15 g of glucose (e.g., 4 ounces of fruit juice). If a patient is not awake, unable to take anything by mouth after the surgery or lacking intravenous (IV) access, 25–50 mL (12.5–25 g) of intravenous dextrose 50% [26] or subcutaneous glucagon 1 mg should be administered [20]. BG testing should be repeated 15 min after initial therapy and repeated if BG remains below 70 mg/dL.

Preoperative Evaluation

Preoperative evaluation should include a thorough history of the patient's type and duration of diabetes, presence of complications, medications, and degree of BG control [27]. Home BG readings and HbA1c should be reviewed to assess potential for hyper- or hypoglycemic episodes in the perioperative period [28]. Perioperative patients are at especially high risk of hypoglycemia in the setting of a prolonged fasting state.

Most recommendations for oral and non-insulin injectable antidiabetic agents are based on pharmacology of medications and outcomes of small studies [1]. Most societies recommend discontinuing oral and non-insulin injectable agents including metformin, glucagon-like peptide-1 (GLP-1) agonists, insulin secretagogues, and thiazolidinediones, on the day of surgery. One exception is sodium-glucose

cotransporter-2 (SGLT2) inhibitors, which should be held for 3–4 days prior to surgery [23, 29]. Recently the American Society of Anesthesiologists (ASA) announced based on anecdotal reports and without clear data a recommendation to withhold weekly GLP-1 agonists 1 week prior to surgery out of concern for delayed gastric emptying and risk of aspiration. Some are concerned about preoperative hyperglycemia that may occur as a result of holding these potent glucose-lowering medications. Of note this recommendation has not been universally accepted [30].

The following provides a summary of preoperative non-insulin diabetes medication management (Table 19.2).

Metformin

The long-standing preoperative recommendation for metformin has been to discontinue its use 48 h before surgery due to the risk of lactic acidosis from perioperative disturbance in renal perfusion. Recent evidence has shown that the use of metformin in the perioperative period did not significantly affect lactate levels in cardiac or noncardiac surgeries in patients with type 2 DM (T2DM) [31, 32]. Thus, guidelines have shifted to stopping metformin on the day of surgery [23] and restart on the day of surgery when normal diet is resumed [20]. Guidelines from a few societies allow for metformin to be continued for specific cases. The AAGBI recommends that metformin be given on the day of surgery if the procedure does not require contrast media. If contrast medium is to be used or if eGFR is detected to be less than 60 mL/

Table 19.2 Perioperative management of oral and non-insulin injectable antidiabetic agents

| Non-insulin diabetes medication | Day(s) before surgery | Morning of surgery |
|---|---|--|
| Metformin | Continue usual dose [20, 23] | Hold [20, 23] |
| Sulfonylureas, meglitinides | Continue usual dose [20, 29] | Hold [20, 29] |
| Sodium-glucose cotransporter-2 (SGLT2) inhibitors | Hold 3 days prior to surgery (For ertugliflozin, hold 4 days prior to surgery) [23] | Hold [23] |
| Glucagon-like peptide-1 (GLP-1) agonists | Continue usual dose [23] *Alternate approach per ASA: weekly GLP-1 hold × 1 week | Hold [23] |
| Dipeptidyl peptidase 4 (DPP-4) inhibitors | Continue usual dose [23] | Debated and may be appropriate to continue in select patients (refer to text) [15] |
| Thiazolidinediones | Continue usual dose [23] | Hold [23] |
| Alpha-glucosidase inhibitors (acarbose) | Continue usual dose [23] | Hold [23] |

min, metformin should be held on the day of surgery and for the following 48 h [16]. If there is severe renal dysfunction (eGFR <30 mL/min) during preoperative evaluation or developed after surgery, metformin should be discontinued until renal function recovers [1].

Sulfonylureas and Meglitinides

Sulfonylureas and meglitinides are insulin secretagogues that stimulate endogenous insulin secretion independent of BG levels and carry risk of hypoglycemia in the fasting state. As such, insulin secretagogues are recommended to be discontinued the day of surgery to minimize the risk of hypoglycemia [20, 29].

Sodium-Glucose Cotransporter-2 (SGLT2) Inhibitors

Prolonged fasting period and surgical procedures increase the risk of SGLT2 inhibitor (SGLT2i)-associated euglycemic diabetic ketoacidosis (EDKA). The ADA guideline recommends stopping SGLT2i 3 days prior to scheduled elective surgery and, in the case of ertugliflozin, 4 days prior [23]. Few organizations have advised a more nuanced approach. For example, the Australian Diabetes Society (ADS) recommends that SGLT2i be stopped for at least 3 days prior to surgery and procedures requiring one or more days in hospital [33]. For colonoscopy requiring bowel preparation with carbohydrate restriction, SGLT2i should be stopped for at least 4 days [33]. If the patient accidentally takes an SGLT2i outside of the recommended time frame, cancellation or postponement of elective surgery should be considered [34]. Alternatively, the patient can be checked for any evidence of DKA prior to and after the procedure.

If a patient who is taking SGLT2i requires an urgent procedure, it should be stopped immediately [35]. EDKA is more common in patients undergoing emergent surgery [36]. Unfortunately, many societies have not yet developed a detailed consensus guidance around the management of patients on SGLT2i requiring urgent procedures. One guideline from the ADS recommends obtaining initial BG and ketone level for any patient who has not stopped SGLT2i therapy prior to any procedure, whether it be urgent or non-urgent [33]. If the BG is within acceptable range, ketones are <1.0 mmol/L, and the patient is clinically well, the procedure can proceed [33]. They also recommend monitoring BG and blood ketone testing every hour during the procedure and every 2 h following the procedure until normal PO intake is resumed [33]. If the blood ketone level is >1.0 mmol/L and the patient is clinically unwell at any point before, during, or after a procedure, an arterial or venous blood gas should be obtained to assess for the presence of DKA [33]. If the patient has DKA or EDKA, then any non-urgent surgery should be postponed, and the intensive care unit and/or endocrinology should be contacted [33]. Specifically for patients with T1DM taking SGLT2i off-label, several protocols have been developed to reduce the risk of DKA which can be extrapolated for guidance in approaching the

patient who has inadvertently taken an SGLT2i before surgery. One example of a published protocol is the STOP DKA Protocol [37]. This protocol provides a useful risk stratification method based on various blood ketone levels for patients experiencing symptoms that are suggestive of DKA. In this protocol, the “normal or mild” category is defined by blood ketone levels <1.0 mmol/L, the “moderate” category is defined as levels $1.0\text{--}1.4$ mmol/L, the “high” category is defined as levels $1.5\text{--}2.9$ mmol/L, and the “extreme” category is defined as ≥3.0 mmol/L [37]. For each ketone level category, there is a tiered approach for supplemental insulin and carbohydrate intake depending on the blood glucose levels, which is recommended to be checked every 2–4 h [37]. If the patient has DKA or EDKA, then any non-urgent surgery should be postponed, and the intensive care unit and/or endocrinology should be contacted [33]. Northwell Health recently developed a preoperative SGLT2i protocol to triage patients who did not hold the medication over the 3–4 day required interval. Serum or point of care ketone levels are used to determine ability to proceed with surgery (low risk), require further workup (intermediate risk) or have surgery cancelled (high risk) and requiring further management for DKA.

Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists

GLP-1 receptor agonists were traditionally discontinued on the day of surgery, however new alternative recommendation by ASA recommend a one week discontinuation for weekly GLP1 agents prior to surgery. These recommendations have not been universally accepted, with different variations being adopted at various institutions. There is not enough data on the use or influence of GLP-1 receptor agonists upon glycemia in perioperative care to recommend its use [23]. However, AAGBI recommends that GLP-1 receptor agonists be continued given the risk of hypoglycemia is low [16]. A randomized controlled trial (RCT) showed that preoperative liraglutide, compared with placebo, reduces insulin requirements while improving perioperative glucose control during cardiac surgery [32]. Another RCT found that perioperative use of exenatide alone or in combination with basal insulin was safe and effective for glucose management of hospitalized surgical patients with T2DM [38]. However, GLP-1 agonists can cause adverse gastrointestinal side effects which may limit its use perioperatively.

Dipeptidyl Peptidase 4 (DPP-4) Inhibitors

The general preoperative recommendation for DPP-4 inhibitors has been to discontinue its use on the day of surgery. The ADA recommends withholding all oral glucose-lowering agents the morning of surgery [23]. The AAGBI, the French Society of Anaesthesia and Intensive Care Medicine (SFAR), and the Association of Anaesthetists of Great Britain and Ireland all recommend DPP-4 inhibitors to be continued on the day of surgery given its low risk of hypoglycemia [16, 19, 39].

Thiazolidinediones

Thiazolidinediones are recommended to be held on the day of surgery to avoid potential fluid retention. The ADA recommends withholding all oral glucose-lowering agents the morning of surgery [23]. AAGBI recommends that pioglitazone be continued on the day of surgery [16].

Alpha-Glucosidase Inhibitors (Acarbose)

The ADA guideline recommends withholding all oral glucose-lowering agents the morning of surgery [40]. AAGBI recommends holding acarbose in the morning if the patient is nil per os (NPO) for morning surgery and continuing the medication in the morning if the patient is eating and scheduled for afternoon surgery [16].

Insulin

Preoperative management for patients with T2DM who are normally treated with insulin is summarized in Table 19.3.

Intraoperative Evaluation

Intraoperative hyperglycemia, defined as BG >180 mg/dL, has been associated with poor outcomes postoperatively. Causes include procedure-related stress, dexamethasone administration (to prevent postoperative nausea and vomiting), inflammation, volatility of anesthetics, and the alteration of glucose metabolism [28]. While exact BG goals differ between organizations, multiple societies including the Endocrine

Table 19.3 Preoperative insulin management for patients with type 2 diabetes

| Type of insulin | Evening before surgery | Morning of surgery |
|---|--|--|
| Basal long-acting and ultra-long-acting insulin | Reduce usual dose by 20–25% [1, 24] | Reduce usual dose by 20–25% [1, 24] |
| Twice daily long-acting insulin | Continue usual dose [1, 24] | Reduce usual dose by 20–25% [1, 24] |
| NPH, premixed insulin | Reduce usual dose by 20% [1] | Reduce usual dose by 50% Hold if morning fasting glucose <120 mg/dL [1] |
| Prandial insulin | Hold when fasting state or bowel prep/clear liquid diet begins [1, 41] | Hold when fasting state or bowel prep/clear liquid diet begins [1, 41] |

Society, SAMBA, and the Society of Critical Care Medicine agree on maintaining intraoperative BG levels below 180 mg/dL [1, 28]. In randomized studies of perioperative BG management, improved perioperative outcomes, survival benefit, and decreased ischemic events were noted when BG was maintained under 200 mg/dL pre-, intra-, and postoperatively [42]. However, intensive glucose-lowering therapy to maintain BG levels between 80–100 mg/dL has been shown to increase the incidence of severe hypoglycemia, death, and stroke [2, 43].

Protocol for management of intraoperative hyperglycemia depends on the duration of procedure, hemodynamic stability, subtype of diabetes mellitus, and preoperative diabetes treatment. However, a review of national and international societies reveals a paucity of clinical guidelines regarding frequency of intraoperative glucose monitoring. In its Consensus Statement, SAMBA recommends q 1–2 hourly monitoring in longer procedures, taking into account the type of insulin the patient has received as well as the amount of insulin (more frequent checks are recommended in patients receiving insulin the morning of the procedure or if their preoperative admitting glucose level was low) [44]. The Academy of Medical Royal Colleges based in the United Kingdom via the Centre for Perioperative Care also recommend a minimum of q 1 hourly BG checks if on insulin infusion while sedated/anesthetized. Included in these guidelines' criteria for starting insulin infusions in surgical patients are anticipating or have an actual fasting period greater than one meal; T1DM patients who have not received background insulin; suboptimal diabetes control (defined as A1c > 8.5%); and most DM patients requiring emergency surgery [45]. These recommendations are outlined in Fig. 19.1.

Authors such as Dogra and Jialal and Galway et al. have recommended similar practice in the operating room. For instance, in surgeries of shorter duration (<4 h), expected hemodynamic stability, or minimal fluid shift, hyperglycemia can be managed with q 2-hourly subcutaneous correctional insulin (preferably rapid-acting insulin) and BG checks. In surgeries of longer duration (>4 h), hemodynamic fluctuations, or massive fluid shifts, hyperglycemia should be managed with intravenous insulin infusion, and BG monitored every 1–2 h [2, 28].

Patients with T2DM treated with lifestyle modification who are undergoing procedures that are less than 2 h should have BG checked preoperatively and shortly after surgery [27, 46]. T2DM patients treated with oral agent/non-insulin injectables require BG checks every 2 h via either arterial or venous blood gas if they are hypotensive, on vasopressors, or critically ill [46]. Correctional short- or rapid-acting insulin should be administered every 4–6 h to correct hyperglycemia [27].

In patients with T1DM or T2DM treated with insulin who are undergoing short, uncomplicated procedures, glucose should ideally be monitored at least every hour (or more frequently if BG levels fall below 100 mg/dL or if the rate of drop in BG is rapid) [47–54]. For rapid-acting insulin, correctional dosing may be calculated using the following equation: (Measured glucose – 100)/insulin sensitivity factor. For patients on insulin at home, insulin sensitivity factor = 1800/patient's total daily

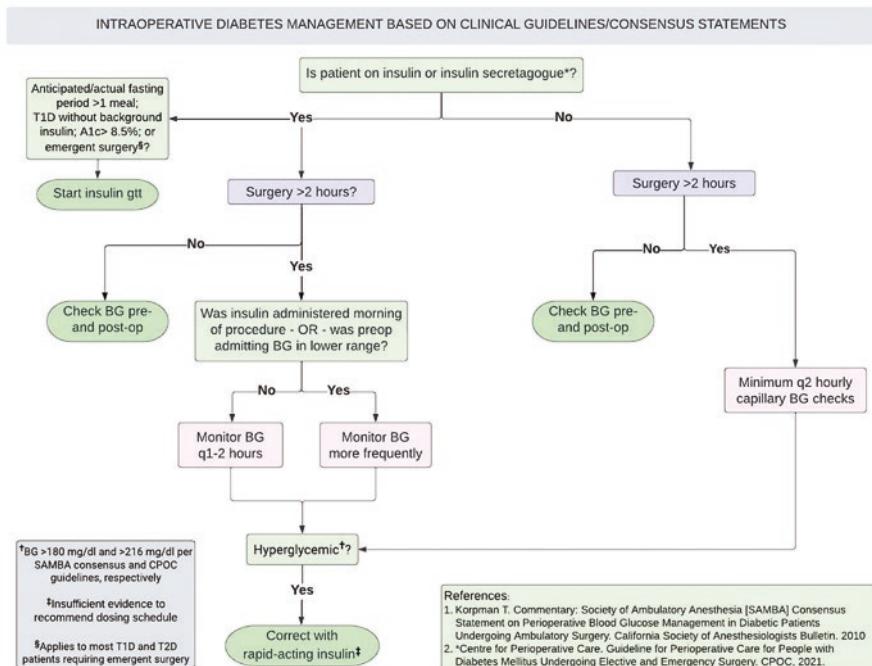


Fig. 19.1 Intraoperative diabetes management based on clinical guidelines/consensus statements [44, 45]. T1D type 1 diabetes mellitus, T2D type 2 diabetes mellitus, gtt drip, BG blood glucose

dose of insulin; if the patient is on oral medication(s) or if the total daily dose is unavailable, then “40” may be used [1]. Additionally, 5% dextrose or 0.45% sodium chloride solution should be started at a rate of 75–125 cc/h in order to prevent the metabolic changes of starvation [48, 49, 52–54].

In insulin-treated T1DM or T2DM patients who are undergoing long and complex procedures (e.g., CABG, transplant, neurosurgical), or who are critically ill, continuous insulin infusion is usually required with BG checks every 1–2 h (by lab or finger stick) [27, 46]. This is due to IV insulin’s ease in titration due to its short half-life, which provides more reliable insulin delivery and consequently more precise glucose control [55, 56]. Subcutaneous insulin, on the other hand, has been associated with marked variability in plasma glucose, which may in part be attributable to the variation in insulin absorption in the setting of hypoperfusion, vasoconstriction, and hypothermia.

Though monitoring intraoperative blood glucose as suggested above represents ideal practice, there are practical challenges to keep in mind. For example, OR staff

must be properly trained in glucometer use; if unable to obtain finger sticks themselves, they may require assistance from staff outside the OR, which may delay glucose measurements. Even with properly trained staff, compliance to such frequent monitoring may be an issue due to greater focus on other components of surgery [57]. BG check reminders may be beneficial to the OR team [58]. This assumes proper insulin management protocols already exist at these institutions. Furthermore, certain procedures (e.g., robotic surgery) may be prohibitive of accessing anatomical sites for frequent BG checks, while placement of arterial lines may be too invasive for certain procedures.

Although more convenient and accurate than current methods of intraoperative BG monitoring, CGM has not thoroughly been tested in the operative setting [28], though it may provide a solution to this dilemma in the future.

Postoperative Evaluation

Postoperatively, BG should be monitored at least every 2 h until the patient is awake and alert. For patients treated with intravenous insulin infusion, it should be continued postoperatively until the patient can tolerate solid food, followed by transition to a subcutaneous regimen. The first dose of subcutaneous insulin must be given before discontinuation of the IV insulin infusion due to the short half-life of IV regular insulin. Long-acting insulin should be given 2 hours prior to discontinuation, particularly for T1DM.

For patients treated with subcutaneous insulin, continue along with IV 5% dextrose to prevent hypoglycemia and reduce stress-related proteolysis and catabolic changes if the patient is not able to resume eating. If the patient is eating, a subcutaneous basal-bolus insulin regimen can be restarted. For patients with T2DM, oral intake is almost always reduced in the hospital compared with the outpatient setting. Therefore, it may be necessary to reduce the typical outpatient dose of basal insulin by about 20–25% in order to prevent hypoglycemia [59].

For patients treated with oral or non-insulin injectable agents, regimen may be resumed once the patient is eating well. However, there are a few caveats to consider. Metformin should not be restarted in the patient with severe forms of renal insufficiency, hepatic impairment, or congestive heart failure. Sulfonylureas should be started only if the patient is eating well. DPP-4 agents may be restarted in the postoperative period when the patient is eating [60, 61]. GLP-1 agonists should not be restarted until nausea and/or vomiting has resolved and the patient is eating well. SGLT2 inhibitors should typically not be restarted in the inpatient setting due to risk of dehydration, volume contraction, and DKA. Thiazolidinediones should not be restarted if the patient develops congestive heart failure or fluid retention or any liver dysfunction.

Correctional doses of short- or rapid-acting insulin may be given to supplement usual pre-meal insulin in patients on a regimen of scheduled basal and prandial insulin to correct pre-meal hyperglycemia. It may be given before meals or every

6 h in patients who are NPO. Sliding scales of correction insulin should not be used as the sole treatment for patients with T1DM or for insulin-treated T2DM. In patients with T2DM treated at home with oral agents or low-dose insulin, a randomized trial comparing basal insulin plus correctional scale, basal-bolus insulin plus correctional scale, and sliding-scale regular insulin alone found that the sliding scale only group had significantly higher mean glucose level [62].

Emergency Surgery

While HbA1c level should also be obtained preoperatively to assess for undiagnosed diabetes and glycemic control, sometimes attaining HbA1c is not feasible in emergent procedures. In cases of emergent surgery, oral and non-insulin injectable antihyperglycemic agents (including SGLT2 inhibitors) should be held immediately [2]. Management for patients who have not discontinued SGLT2 inhibitors and require emergent surgery is detailed earlier. Should DKA or EDKA develop in these patients, it should be managed accordingly with IV insulin infusion and dextrose infusion, with monitoring of anion gap, serum ketone, and arterial pH [35]. Additionally, if a patient is on an insulin pump, the pump should be discontinued immediately, and the patient should be started on a continuous insulin infusion, titrated according to BG levels [28]. Patients in whom BG is very high or with hypoglycemia should have BG monitored more frequently [17, 63].

Management of Type 1 Diabetes in the Perioperative Period

Special attention should be paid to patients with T1DM undergoing surgery as glucose metabolism can be significantly altered depending on factors such as duration of fasting, anesthesia, and stress. Withholding oral intake will decrease insulin requirements, and stress will increase insulin requirements. If the procedure requires a period of fasting, BG monitoring should be performed every 1–2 h, and the goal is to maintain BG levels between 100 and 180 mg/dL and avoid development of both hypoglycemia and ketoacidosis [48].

For short procedures less than 2 h, usual basal rates or doses can be continued. During and after the procedure, rapid or short-acting insulin can be used to provide additional insulin needs as determined by BG measurements. Intravenous dextrose should be initiated if BG level decreases. For procedures that are prolonged, infusion of intravenous insulin along with 5% dextrose with electrolytes should be started. BG monitoring should be performed every 1–2 h and insulin infusion rate adjusted to avoid either hypo- or hyperglycemia. The BG level should be maintained between 100 and 180 mg/dL [48]. Postoperatively, home insulin regimen can be resumed if the patient tolerates oral intake. More frequent BG testing is recommended for 24–48 h after the procedure due to increased risk of hyperglycemia.

Diabetes Technology in the Perioperative Period

Continuous Glucose Monitoring System (CGM)

Study on CGM use in surgery is limited. A pilot prospective study of ten patients with diabetes undergoing elective surgery showed the mean absolute relative difference (MARD) of 9.4% for CGM values compared with the point of care glucose levels postoperatively, suggesting reliability of CGM glucose [64]. Various conditions that can potentially interfere with the accuracy of CGM include magnetic resonance imaging (MRI), computed tomography (CT) scan, high-frequency electrical heat (diathermy) treatment, shock requiring vasopressor therapy, and hypoxia. One study in Switzerland evaluated the performance of DEXCOM G6 during elective abdominal surgery and showed that DEXCOM G6 was consistent and had acceptable accuracy during surgery [65]. Another study evaluated the performance of CGM in patients without diabetes undergoing coronary artery bypass surgery. The result demonstrated that CGM is less reliable in the operating room with increasing patterns of signal loss during surgery, but CGM postoperatively showed adequate and sustained accuracy [66]. A Japanese study evaluated the performance of the FreeStyle Libre system for patients with T1DM undergoing cardiac surgery. Glucose values from CGM were used to adjust to insulin dosage and generally correlated with venous BG level [67].

Due to limited studies, real-time CGM devices such as DEXCOM were initially recommended to be removed prior to MRI or high-frequency electrical heat (diathermy) treatment that is unrelated to a Bovie or other electrocautery instruments used in the OR. However, one recent study investigated the safety and functional integrity of CGM after simulated radiologic procedures such as MRI and concluded that DEXCOM G6 was able to retain basic function and data integrity after exposure [68]. It is safe to use during CT scan. Other systems such as Guardian Sensor 3 and 4 should not be exposed to MRI equipment, diathermy devices, or other devices that generate strong magnetic fields such as X-ray, CT scan, or other types of radiation. FreeStyle Libre should also be removed prior to MRI, CT scan, X-ray, or diathermy treatment. Its functionality during electrocautery has not been tested. Of note, as more research occurs, appropriate continuation of these devices in more settings may be more formally expanded as traditional restrictions are being re-evaluated and clarified.

Continuous Subcutaneous Insulin Infusion (Insulin Pump)

The decision whether to continue insulin pump in surgery depends on several factors including duration of procedure, placement of insertion sites relative to the surgical field, provider's comfort level, patient's preference, and patient's alertness postoperatively to resume self-management.

For ambulatory or short surgical procedures other than cardiac or neurosurgical procedures, patients can continue to use their insulin pump as long as they will be awake after the procedure and the pump insertion site is away from the field of surgery. A temporary basal infusion rate reduction of 20–50% 2 h pre-procedure and up to 4 h postoperatively may be appropriate depending on glucose level. For longer duration surgical procedures or complex procedures under general anesthesia (such as coronary artery bypass graft, renal transplant, or prolonged neurosurgical operations), patients have limited or no ability to operate the insulin pump independently postoperatively. Therefore, it is advisable to transition off the pump with administration of basal insulin 2 h prior to pump discontinuation or use intravenous insulin infusion. The dose should be based on the programmed pump setting. Before surgery, the patient should ensure that the catheter and pump can be stored safely. If no basal insulin was given prior to surgery, continuous insulin infusion can be started intraoperatively and glucose monitored.

Enhanced Recovery After Surgery (ERAS) Protocol for Patients with Diabetes

ERAS pathway is an evidence-based multimodal perioperative approach designed to achieve early recovery by maintaining preoperative organ function and reducing the stress response following surgery. One component of the ERAS pathway proposes preoperative oral administration of clear fluid containing a high carbohydrate load 2–3 h before anesthesia. This aims to reduce the insulin resistance and catabolic state induced by surgical stress. Several RCTs have demonstrated benefits and improved patient outcomes of oral carbohydrate loading in patients without diabetes, including significant reduction in insulin resistance and improvement in patient well-being after surgery, especially hunger, thirst, malaise, anxiety, and nausea [69]. The use of oral carbohydrate loading in patients with diabetes has been debated. Potential risks are pulmonary aspiration due to delayed gastric emptying in certain patients with diabetic neuropathy [70] and perioperative hyperglycemia and its associated postoperative complications. Due to these hypothetical risks, patients with diabetes have also been excluded from the majority of the studies evaluating ERAS.

Overall, the published ERAS guidelines for various types of surgery were unable to make recommendations regarding preoperative carbohydrate loading in patients with diabetes due to insufficient supporting evidence [71], do not recommend its use [72, 73], or do not comment on its use for diabetes [74, 75]. The Endocrine Society recommends against the use of preoperative carbohydrate loading in adult patients with T1DM, T2DM, or other forms of diabetes undergoing surgical procedures [15]. Until further research and evidence is available to inform this decision, it is prudent to avoid preoperative carbohydrate loading in patients with diabetes.

Conclusion

In patients with DM requiring surgical procedures, appropriate glucose management is essential for optimization of clinical outcomes. The goals of perioperative DM management include avoidance of hypoglycemia, prevention of DKA or hyperosmolar states, and minimizing hyperglycemia. Most oral or non-insulin injectable diabetes medications are held on the day of or prior to surgery due to concern for potential hypoglycemia, metabolic derangements, or gastrointestinal side effects, especially SGLT2 inhibitors which should be held 3–4 days prior to the scheduled procedure. Intraoperative management requires frequent monitoring of BG levels and insulin strategies depending on the duration of procedure, hemodynamic stability, subtype of DM, and preoperative DM treatment. Postoperatively, it is important to allow a safe transition to subcutaneous basal/bolus insulin regimen when patients are ready to resume PO intake. Optimal perioperative diabetes management is achievable but requires careful coordination among staff and providers from outpatient primary care, surgery, endocrinology, internal medicine, and critical care medicine.

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Chapter 20

Hyperglycemia and Diabetes in the Posttransplant Patient



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Introduction

In 2018, Global Observatory of Donation and Transplantation reported 140,964 organ transplants worldwide [1]. Immunosuppressive regimens and improved perioperative care have improved graft as well as patient survival after transplantation in the long term [2]. However, immediately after the procedure, hyperglycemia is common. Many patients who undergo transplant may also have preexisting diabetes which was the cause of the chronic organ failure. Similarly, end-stage organ failure, as seen with kidney, liver, and heart transplant, may itself contribute to glucose dysregulation. Patients may also be diagnosed with diabetes after transplantation, and some of them may also have previously unrecognized diabetes, which is called posttransplantation diabetes mellitus (PTDM). In any postoperative patient, many factors such as pain, release of cytokines, and counterregulatory hormones can cause insulin resistance and affect insulin action [3]. Postoperative insulin secretion

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has been linked to preoperative insulin resistance. A study of elective colorectal surgery showed that in patients with low insulin sensitivity preoperatively, postoperative insulin secretion is decreased compared to those with normal insulin sensitivity [4]. Additionally, glycemic management in posttransplant recipients is further complicated by the unpredictable function of the transplanted organ, use of immunosuppressive agents that cause both insulin resistance and insulin deficiency, as well as variable nutritional status and carbohydrate intake [5].

Despite this complex postoperative state, it is important to manage hyperglycemia in the posttransplant patient. In nontransplant patients, numerous studies have linked postoperative tight glycemic control with reduced total postoperative infection rates and short-term mortality [6]. Similar outcomes were also observed for patients with and without diabetes after heart transplant [7]. On the other hand, hypoglycemia from very tight glycemic control may also cause harm, as demonstrated in the NICE-SUGAR study of critically ill patients who had higher mortality with lower glucose targets [8]. Hypoglycemia is also a potential serious perioperative complication and may be masked in the immediate postoperative period when the patient is still recovering from the effects of anesthesia. To add further complexity to the postoperative course of transplant patients, there are unprecedented changes in organ function unique to transplantation as well as the aforementioned variable nutrition and rapidly changing corticosteroid dosing, all of which contribute to highly variable fluctuations in glucose. The balance of these multiple changing variables that cause both hyperglycemia and hypoglycemia presents a tremendous challenge for the clinicians in the hospital setting.

Optimizing posttransplant management of patients with diabetes has been linked to improved outcomes [9]. Inpatient management of diabetes by specialized teams have shown to improve quality of care, reduce inpatient cost, improve transition of care, and decrease 30-day readmission [10, 11]. Although the literature is not yet robust enough in posttransplant glucose management as in other inpatient populations, we will review the available data and provide clinical expertise to guide posttransplant glucose management in the hospital setting.

Terminology

There are several terms that are used to refer to diabetes or hyperglycemia in the posttransplant setting. In 2014, an international consensus meeting revised the previous term new-onset diabetes after transplantation (NODAT) to posttransplantation diabetes mellitus (PTDM) because it describes the diagnosis of diabetes after transplant, irrespective of timing or if it was present but undiagnosed prior to transplant [12]. NODAT was discouraged because often diabetes is not recognized prior to transplantation and then unmasked in the posttransplant state. Transient posttransplant hyperglycemia is another condition that occurs in the immediate-to-early posttransplant setting, generally as a result of postsurgical stress and the administration of high-dose glucocorticoids. These patients may not progress to a diagnosis of

PTDM as the hyperglycemia resolves within the first few weeks after transplantation.

Epidemiology

Diabetes is a common complication after transplantation and is associated with increased morbidity and mortality. Even transient perioperative hyperglycemia is linked to a higher incidence of PTDM. Studies have shown that up to one-third of kidney transplant recipients without prior diabetes develop PTDM by 6 months posttransplantation [13–16]. The incidence of PTDM in the literature varies widely from 5 to 50% and by organ type as well as race/ethnicity with Hispanic and African-American races having the highest risks [17].

Other long-term studies have shown 2- to 5-year incidence rates ranging from 18 to 33% [18, 19]. Data from the Organ Procurement and Transplant Network/Scientific Registry of Transplant Recipients (OPTN/SRTR) showed that the prevalence of PTDM at 1-year posttransplant decreased from 10% in 2007 to under 4% in 2016, while the 5-year incidence of PTDM decreased from approximately 16% in 2007 to 10% in 2012 [20, 21]. However, a lack of consensus on the diagnostic criteria used for PTDM for many years contributes to this wide variance in the historical data.

Risk Factors

Risk factors for PTDM can be categorized into those that are modifiable and non-modifiable and are summarized in Table 20.1 [2, 22–38]. Nonmodifiable risk factor are similar to those of type 2 diabetes and include the following: age ≥ 40 to 45 years, African American race, Hispanic ethnicity, history of gestational diabetes or family history with a first degree relative with type 2 diabetes, preexisting impaired glucose tolerance or prediabetes, increased human leukocyte antigen (HLA) mismatching, male gender, and deceased-donor allografts. Although controversial, a prior diagnosis of polycystic kidney disease may also be associated with PTDM [22]. Other genetic factors may also be associated with PTDM, but routine genetic testing is not recommended [23].

The modifiable risk factors can be categorized into several areas: types of immunosuppressive medications used, presence of overweight/obesity or posttransplant weight gain, physical inactivity, certain viral infections, and possibly some electrolyte/nutrient deficiencies.

There are several classes of immunosuppressive agents used posttransplant, and each class has varying glucometabolic effects. Glucocorticoids (GC) are an important part of any immunosuppressive protocol both in the induction and maintenance phases. They are also frequently used in graft rejections [24]. Biological effects of

Table 20.1 Risk factors for development of posttransplant diabetes mellitus [2, 22–38]

| | |
|---|---|
| Factors unrelated to transplantation | Older age Male gender South Asian/African-Caribbean ethnicity Sedentary lifestyle Overweight/obesity Genetic factors Strong family history Gestational diabetes Adult polycystic kidney disease (Controversial) Interstitial nephritis Preexisting impaired glucose tolerance test Prediabetes |
| Factors associated with transplantation | Glucocorticoids Calcineurin inhibitors (tacrolimus > cyclosporine) Hepatitis C or cytomegalovirus infection Posttransplant weight gain Deceased donor allograft Increased human leukocyte antigen mismatching |

GCs are determined by daily dose and the patient's sensitivity to them [25]. High-dose GC which is commonly used in immediate posttransplant period has a much more intense impact on glycemic control than chronic low-dose maintenance dose [26]. It is suggested that genetic variability in GC pathway may play some role in the development of PTDM with some polymorphisms being significantly associated with PTDM and some being associated with higher serum glucose but not higher risk of PTDM at the end of the first posttransplant year [25]. Corticosteroids cause hyperglycemia predominately by decreasing peripheral glucose uptake, increasing hepatic gluconeogenesis, and, in long-term, stimulating appetite and promoting weight gain [2, 26].

Another class is the calcineurin inhibitors, of which the most often used are tacrolimus and cyclosporine. Both of these drugs increase the risk of PTDM, with tacrolimus being the most diabetogenic in the class [27]. An increased tacrolimus level (>15 ng/mL) has been strongly associated with impaired glucose tolerance and PTDM [28, 29]. There is no difference in the incidence rate between extended release and immediate release tacrolimus formulations [30]. These drugs cause swelling, vacuolization, and reversible toxicity to islet cells in the short term to reduce insulin secretion and beta cell apoptosis that causes more permanent insulin deficiency [31]. In the early periods after transplant, these drugs are generally dosed to maintain a higher plasma level than later periods posttransplant and cause hyperglycemia in proportion to dose exposure of the drug.

Another commonly used immunosuppressive agent in the regimen is mycophenolate mofetil (MMF), but it does not have any effects on glucose metabolism. Additionally, azathioprine and belatacept, which are used more infrequently, are also not associated with increased risk of PTDM [32].

Preexisting patient factors also play a role in the development of PTDM. An impaired glucose tolerance test prior to the transplant or an abnormal OGTT at

3 months posttransplant are associated with an increased risk of developing PTDM [33, 34]. Not surprisingly, the association of preexisting obesity (body mass index $\geq 30 \text{ kg/m}^2$) and development of PTDM has been shown in several different studies [27, 32]. Additionally, certain viral infections such as hepatitis C (HCV) and cytomegalovirus (CMV) are associated with both pre- and posttransplant diabetes [32, 35]. Low serum magnesium level has been shown to be associated with development of diabetes in general population, but the data is controversial among transplant population [36, 37]. Vitamin D deficiency ($\leq 10 \text{ mg/mL}$) pre-transplant has also been shown to be an independent risk factor for PTDM after kidney transplantation [38].

Evaluation and Diagnosis of PTDM

Transient posttransplant hyperglycemia is very common within the immediate posttransplant window; however it resolves in many cases within the first few weeks [12]. It is recommended not to make a formal diagnosis within the first 6 weeks after transplantation and until the dose of immunosuppressant medications are stable and there is no acute infection [12]. In 2003, the diagnosis of diabetes after transplantation was standardized using the World Health Organization (WHO) and the American Diabetes Association (ADA) criteria and has remained synchronous with these organizations since that time [39]. PTDM is currently diagnosed by any of the following: (1) symptoms of polyuria, polydipsia, unexplained weight loss, and a random plasma glucose $\geq 200 \text{ mg/dL}$; (2) fasting (at least 8 h) plasma glucose (FPG) $\geq 126 \text{ mg/dL}$, confirmed by a second testing; (3) oral glucose tolerance test (OGTT) performed with 75 g of glucose load and a glucose level $\geq 200 \text{ mg/dL}$ at 2 h post ingestion; or (4) A1C $\geq 6.5\%$, 3 or more months posttransplant. The A1C test is not recommended for diagnosing hyperglycemia during the first 3 months after transplantation. This is because certain factors, such as anemia of chronic disease, blood transfusion, and high-dose immune suppression, can affect the glycosylation of hemoglobin, which in turn affects the accuracy of the test. It takes at least 3 months for new hemoglobin to be formed and glycated, so waiting until this time has passed allows for a more reliable A1C measurement [39]. Prediabetes includes impaired fasting glucose and/or impaired glucose tolerance and is diagnosed by a fasting plasma glucose between 100 and 125 mg/dL or a 2-h plasma glucose between 140 and 199 mg/dL during an OGTT, respectively, in accordance with the American Diabetes Association (ADA) guidelines. An A1C of 5.7–6.4% is also consistent with a diagnosis of prediabetes [40, 41].

However, these traditional testing methodologies may not have the same sensitivity and specificity in the transplant patient. Initially posttransplant, a fasting plasma glucose weekly during the first 4 weeks, then at 3 and 6 months after transplant, and annually thereafter is recommended. However, some recommend replacing an afternoon glucose level with fasting as it might be more sensitive when level is $\geq 200 \text{ mg/dL}$ [41]. A study of 263 kidney transplant patients comparing FPG,

A1C, and the 2 h OGTT to diagnose PTDM demonstrated that over 24 months, up to 69% of patients meeting criteria for PTDM by the 2 h glucose value on OGTT would have not met the threshold for diagnosis by FPG or A1C [42]. Therefore, the OGTT is recommended as the gold standard for diagnosis of PTDM due to the predominant effects of GC on postprandial glucose over fasting glucose [22, 43].

Inpatient Management of Hyperglycemia Posttransplantation

Glucose Targets

The optimal glucose target in the posttransplant period is not yet established. In general critically ill patients, the American Diabetes Association guidelines recommend using intensive insulin therapy to achieve a target blood glucose values of 140–180 mg/dL in most critically ill patients, whereas more stringent goal such as 110–140 mg/dL may be appropriate for select group of patients including postsurgical patients, as long as these targets can be achieved without significant hypoglycemia [44]. Since data is very limited in transplant patients, these are the same targets employed for critically ill posttransplant patients.

In the non-ICU setting, the Endocrine Society and the AACE Practice Guidelines recommend a pre-meal glucose of <140 mg/dL and a random glucose of <180 mg/dL for the majority of non-critically ill patients treated with insulin [45, 46]. More recently the American Diabetes Association has recommended that target glucose for most general medicine and surgery patients in non-ICU settings should be between 140 and 180 mg/dL [47].

Intraoperative Management

In nontransplant patient, intraoperative strict glycemic control has not been shown to have benefit [48, 49]. There is even more limited data on intraoperative glycemic control for patients undergoing transplantation. One study in liver transplantation of strict (target blood glucose 80–120 mg/dL) versus conventional (target blood glucose 180–200 mg/dL) glycemic targets intraoperatively did not show a statistically significant difference in patient survival or graft survival at 1, 3, or 5 years post-transplantation [50]. Therefore, as in nontransplant patients, a reasonable intraoperative appropriate glucose target is 140–180 mg/dL in patients with and without diabetes. In patient with diabetes where the glucose is above this target, an IV bolus of 5 units of regular insulin, followed by insulin infusion titrated to 140–180 mg/dL protocol, is recommended [51]. In patients without diabetes and a glucose level above target, an IV bolus of 2 units of regular insulin followed by hourly blood glucose monitoring is appropriate [51].

Immediate (<1 Week) Posttransplantation

Management of the glucose targets described above is most often achieved with insulin therapy during this immediate postoperative period. It is important to note that a more stringent target can increase risk of hypoglycemia and does not decrease the incidence of delayed allograft function [52].

(a) Critically ill patients:

Intravenous insulin infusion therapy is utilized when the patient develops hyperglycemia (blood glucose ≥ 180 mg/dL) [51]. Even though optimal targets for glycemic control have not been established, many transplant centers target blood glucose readings between 140 and 180 mg/dL in patients who are critically ill and receiving an insulin infusion [52]. A more stringent target of 110–140 mg/dL can be used if it can be achieved safely without hypoglycemia.

(b) Noncritically ill patients:

After patients are more stable and no longer critically ill, insulin infusion should be transitioned to subcutaneous (SC) insulin infusion. Several factors play a role in calculating the dose of SC insulin: glucocorticoid dose and schedule, allograft function, concurrent infection, and nutrition intake (e.g., NPO, enteral or parenteral nutrition). Glycemic targets among this population include a fasting glucose level < 140 and a random glucose level < 180 [53]. It has been postulated that early insulin therapy has a protective effect against toxic effects of immunosuppressive therapy and inflammatory stress and reduces the risk of PTDM by 73% within the first year after transplant [54].

Due to its pharmacokinetic profile, NPH insulin used with corticosteroids improves glycemic control [55, 56]. In a study including 60 subjects with chronic obstructive pulmonary disease who were admitted to the hospital, those who were treated with insulin NPH for steroid-induced hyperglycemia required lower total daily dose of insulin and lower bolus insulin and did not show a higher rate of hypoglycemia compared to the group that received insulin glargine [57]. For patients on an oral diet, rapid-acting bolus insulin with each meal can be added along with a correction scale as is the usual care for non-transplant hospitalized patients with hyperglycemia and/or diabetes.

Upon Discharge and 1–6 Weeks Posttransplantation

It is recommended that at least twice daily glucose monitoring before breakfast and in the afternoon be continued upon discharge in patients with persistent hyperglycemia who required insulin therapy during admission. Further testing can be suggested in cases of more severe hyperglycemia [41].

For patients with persistent hyperglycemia or preexisting diabetes, insulin regimens with basal and bolus dosing remains the treatment of choice in the first

1–2 months after transplantation. In 2012, Endocrine Society Guidelines Management of non-critically ill patients recommended use of basal bolus insulin regimen over sliding scale insulin regimen due to findings of two landmark trials (RABBIT 2 and RABBIT 2 surgery) [45, 58, 59]. However, there are several variables that providers need to consider when selecting appropriate insulin therapy for inpatient hyperglycemia. A “real-world” study evaluating different insulin strategies to manage hyperglycemia in non-critically ill patients showed that initial therapy with basal bolus regimen was associated with more hypoglycemia and fewer euglycemic days compared to sliding scale regimen [60]. On the other hand, basal only regimen has fewer hyperglycemic episodes and more euglycemic days compared to sliding scale regimen [60, 61].

The 2014 international consensus meeting on PTDM recommended that insulin treatment be continued upon discharge in patients who require at least 20 units of total daily dose of insulin in the immediate posttransplant period. The preferred insulin is insulin NPH to be administered at the same time as the morning glucocorticoid, and the dose should be adjusted based on afternoon glucose levels [62]. This timing matches the typical afternoon hyperglycemia which is commonly observed among patients with glucocorticoid-induced hyperglycemia [63]. Similar to non-transplant patients, insulin glargine is an alternative to NPH, and the dose should be adjusted based on the fasting glucose level. Prandial insulin can be added to both regimens if daytime postprandial hyperglycemia is present, and dose should be calculated based on anticipated carbohydrate ingestion [60, 61]. Further studies are needed to evaluate the efficacy and safety of other long-acting insulins among patients with posttransplant hyperglycemia. When the total daily dose of insulin is decreased to less than 20 units per day, transitioning to oral therapy can be considered [12].

In patients with insulin requirements of less than 20 units per day in the immediate posttransplant period, oral hypoglycemic agents can be considered. Preferred agents with lower risk of hypoglycemia include meglitinides (e.g., repaglinide) [64] or dipeptidyl peptidase 4 (DPP-4) inhibitors (e.g., sitagliptin, linagliptin, saxagliptin, alogliptin) [45].

Many oral hypoglycemic agents may not be safe to use early in the hospital course due to rapidly changing clinical status of these patients. Metformin has the usual limitations of fluctuating renal function which is often the case not only in kidney transplant patients but also other organ transplant affected by medications, hemodynamics, and acute illness [65]. Sulfonylurea class also has the risk hypoglycemia which is considerable given the alterations in renal function as well as variable nutritional status posttransplant [66].

Eight Weeks Posttransplantation and Beyond

Once the patient has stabilized and fully recovered from the surgery and has stable graft function and immunosuppressive regimen, other agents can be considered for chronic management of diabetes. Similar to the chronic management of nontransplant type 2 diabetes, other oral agents may be added such as metformin, sulfonylureas, pioglitazone, and DPP4-inhibitors. However, as with nontransplant patients, these oral agents are not recommended in the inpatient setting due to their many limitations in safety as well as efficacy in this setting [43, 45]. Some noteworthy classes of drugs gaining increasing attention in the chronic management of PTDM are described in greater detail below and may be encountered in the inpatient setting.

Sodium-Glucose Co-transporter 2 Inhibitors (SGLT2 Inhibitors)

Cardiovascular disease remains one of the leading causes of mortality in posttransplant patients [67]. Sodium-glucose co-transporter 2 (SGLT2) inhibitors decrease blood glucose by promoting glucose excretion in the urine and have been shown to have beneficial effects on heart and kidneys in patients with or without diabetes mellitus (DM) [68]. These agents also improve outcomes in patients with heart failure with preserved or reduced ejection fraction [68]. SGLT2 inhibitors exert their beneficial effects by increasing diuresis, restoring tubuloglomerular feedback, decreasing intraglomerular pressure, and minimizing albuminuria [69]. Despite the lack of SGLT2 receptors on the heart, direct effects have also been reported in cardiomyocytes and endothelial cells of the blood vessels [70]. However these clinical benefits can be translated to posttransplant patients and if so, when these agents should be initiated after transplant, remains to be elucidated.

Outcomes and safety profile of SGLT2 inhibitors have been most extensively studied in the kidney transplant recipients with DM. Several studies and case series have shown improvements in A1C, body weight, and blood pressure in this group [67]. Most of these studies included patients who received transplant 3 months to 19 years prior to starting SGLT2 inhibitors. To date, there is only one randomized controlled trial (RCT) of 44 kidney transplant patients which showed that use of empagliflozin was associated with improvement in A1C and body weight without any effect on estimated glomerular filtration rate (eGFR) or blood pressure [71]. This study included patients who received transplant more than 1 year prior to starting SGLT2 inhibitors. A more recent retrospective multicenter study that evaluated 226 post kidney transplant recipients who were prescribed SGLT2 inhibitors for at least 90 days reported that composite outcome of all-cause mortality, death-censored graft failure, and serum creatinine doubling was significantly lower in the SGLT2 inhibitor recipients in a multivariate model (adjusted hazard ratio 0.43, $p = 0.006$) [72]. In this study, 168 patients had DM prior to receiving transplant and 58 developed diabetes after transplant. Of note, 15.6% patients in this study developed a

drop in eGFR during the first month of SGLT2 inhibitor use, but the eGFR recovered thereafter. Shorter time from transplantation and higher mean tacrolimus levels were associated with reduction in GFR. SGLT2 inhibitors have also been studied in heart transplant recipients with DM and have shown to reduce body weight and blood pressure, but no effects were seen on A1C or eGFR [73, 74]. A more recent study looked at the effects of combination SGLT2 inhibitors and GLP-1 agonists on heart transplant recipients and showed improvements in A1C and body weight and no change in eGFR [75]. Mean time from transplant was 5.5–10.1 years in these studies. Data on use of SGLT2 inhibitors for PTDM management among recipients of pancreas, lung, liver, and bone marrow transplants is less robust if not at all available. SGLT2 inhibitor use is not without risks. Most common reported adverse events include urinary tract infections and genital mycotic infections with non-hyperglycemic diabetic ketoacidosis being an uncommon but notable occurrence [67]. Large RCTs with long-term followed up are needed to further understand cardiorenal protective effects of SGLT2 inhibitors among posttransplant recipients with and without DM.

Incretin Therapies

Both glucagon-like peptide-1 (GLP-1) and dipeptidyl peptidase 4 (DPP-4) inhibitors stimulate insulin secretion in a glucose-dependent fashion and have reduced risk of hypoglycemia. Glucagon-like peptide-1 receptor agonists (GLP-1RA) has been shown to improve glycemic control, lower blood pressure, and reduce body weight and may also have beneficial effects on cardiovascular and renal systems in nontransplant patients. Studies on GLP-1RA have suggested their role in counteracting drivers of immunosuppressant-induced beta cell dysfunction.

GLP-1RA improve both first- and second-phase insulin secretion and restore beta cell sensitivity to glucose, and both GLP-1 RA and DPP-4 inhibitors inhibit pancreatic beta cell apoptosis and stimulate the proliferation and differentiation of insulin-secreting beta cells [76]. With these physiological and clinical effects, GLP-1 RA and DPP4-inhibitors may serve as ideal agents for management of PTDM and obesity in the posttransplant patient, but evidence for safety and efficacy in this population is very limited at this time. Table 20.2 summarizes the use of non-insulin treatments for posttransplant hyperglycemia during the immediate, 1–6 weeks, and 8 weeks and beyond posttransplantation periods [64–76].

Table 20.2 Non-insulin treatment of posttransplant hyperglycemia after transplant [64–76]

| Medication | Immediate | 1–6 weeks posttransplantation | Six months posttransplantation and beyond |
|------------------|-----------|-------------------------------|---|
| Meglitinides | No | Yes | Yes |
| DPP-4 inhibitors | No | Yes | Yes |
| Metformin | No | No | Yes |
| Sulfonylurea | No | No | Yes |
| SGLT2 inhibitors | No | No | Yes |
| GLP-1RA | No | No | Yes |

Continuous Subcutaneous Insulin Infusion (CSII)

CSII via an insulin pump or hybrid closed loop system (HCL) is growing in utilization for management of type 1 and type 2 diabetes in nontransplant patients. Whether or not CSII can achieve better glycemic control in PTDM than subcutaneous injections has been studied in some clinical trials.

In a randomized controlled trial study, it was suggested that management with the CSII should ideally reflect the different pathophysiological and metabolic disturbances commonly seen in solid organ transplant recipients. In patients with PTDM, glucose levels are lowest between 2:00 and 8:00 and highest between 14:00 and 20:00 as a result of pharmacokinetics of steroids administered in the morning. Based on this study, administration of the maximal insulin dose in insulin pump during the afternoon showed improvement in the daily glucose profiles compared to a basal subcutaneous insulin in kidney transplant recipients without a previous history of DM [77]. More studies are needed in order to evaluate the role of newer automated insulin delivery systems available now in management and prevention of PTDM.

Diabetic Ketoacidosis Due to Tacrolimus

It is well recognized that tacrolimus decreases insulin secretion, promotes beta cell apoptosis, and causes an insulin-deficient state. Transplant patients on tacrolimus had increased risk of DKA compared to cyclosporine-based immunosuppressive regimens [78]. There is evidence suggesting tacrolimus causes more severe swelling-vacuolization, endoplasmic reticulum stress, and apoptosis of pancreatic islet beta cells. The fact that insulin requirement decreases significantly after DKA resolution and tacrolimus dose adjustment indicates the effect of tacrolimus on DKA development is dose dependent and reversible [78].

Glycemic Control After Pancreas Transplantation

Simultaneous pancreas and kidney (SPK) transplantation may be performed, particularly for those with type 1 diabetes. Unlike islet cell transplantation which is currently performed only in approved centers and under investigational protocols, whole organ pancreas transplantation when successful does not necessitate glucose management as euglycemia is seen immediately post implantation. However, intensive glucose monitoring protocols must be in place to identify any graft dysfunction immediately postoperatively. Graft function can also be monitored with C-peptide, insulin, and proinsulin levels. Due to the systemic (rather than portal) venous drainage of the allograft, basal peripheral insulin concentrations are two to three times higher than with a native pancreas [79]. While each transplant center has its own protocol, typically glucose monitoring is performed hourly for the first 48 h and then every 4 h if glucose values are in the normal range followed by the usual before meals and bedtime when the patient begins an oral diet. With a successful pancreas transplant, hyperglycemia is not seen. However, immediate graft dysfunction or loss can occur with thrombosis in the graft. In these cases, severe hyperglycemia ensues, often rapidly, and insulin therapy is essential. Mild hyperglycemia may also be seen during the period of high doses of corticosteroids. Although there is no published guidance on management of postoperative mild graft dysfunction, our center has a protocol to initiate thiazolidinediones and/or DPP4-inhibitors which are safe and do not have contraindications with graft function and other transplant medications. In the posttransplant period, graft function can be assessed with the criteria outlined in Table 20.3 [80].

Conclusion

Management of hyperglycemia post organ transplantation is challenging with factors such as critical illness, fluctuating allograft as well as other organ function, high-dose corticosteroid therapy as well as other diabetogenic immunosuppressive medications, and highly variable nutrition. It is undoubtedly the most complex patient population for glycemic management and has the least guidance in the

Table 20.3 Assessment of pancreas transplant graft function [80]

| Characteristics | Optimal | Adequate | Marginal | Failed |
|--|-----------------|--|--------------------|---------------------------|
| HbA1c (%) | $\leq 6.5\%$ | $< 7\%$ | $\geq 7\%$ | – |
| Severe hypoglycemia | Absent | Absent | Present | – |
| Insulin requirements | No requirements | $> 50\%$ reduction/ < 0.5 units/kg/day | $< 50\%$ reduction | – |
| C-Peptide level compared to pre-transplant | Increased level | Increased level | Increased level | No significant production |

literature, especially in the acute inpatient setting. However, the evidence and principles of nontransplant inpatient glucose management can be applied as we have outlined. Insulin therapy has been the treatment of choice in the immediate post-transplant period. Non-insulin therapies such as DPP4-inhibitors are the most studied and demonstrate safety and efficacy with the potential to replace or reduce insulin requirements in some situations [81]. Studies are ongoing to evaluate GLP-1 RA and SGLT2 inhibitors, especially for their cardiovascular and renal benefits proven in nontransplant patients. Since PTDM negatively affects survival and increases morbidity and mortality related to cardiovascular events, infections, and graft function, patients should be actively screened and managed with a structured approach. Further research in PTDM prevention and therapies are still needed to guide diabetes management in posttransplant patients.

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Chapter 21

Glycemic Management in Coronary Artery Bypass Graft Patients



Vincent Cascio and Aren Skolnick

Introduction

Coronary artery disease (CAD) is a major cause of morbidity and mortality among diabetes mellitus (DM) patients, who demonstrate an increased risk and faster progression of CAD compared to patients without DM, as well as increased incidence of multivessel disease [1]. Over one-third of people undergoing coronary artery bypass graft (CABG) surgery have DM [2]. Hyperglycemia is common in the perioperative period and occurs with and without DM. Both hyperglycemia and diabetes are independently associated with poor surgical outcomes in patients undergoing CABG surgery, and optimal glucose control is important to achieve the best possible outcomes. In this chapter, we review the pathophysiology of hyperglycemia in critical illness, distinguishing between patients with and without DM. We also review the historical perspective, recent literature, and recommended strategies for the management of hyperglycemia in patients undergoing CABG surgery.

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Pathophysiology

Glucose is the preferred form of energy during critical illness, and the stress response induces hyperglycemia via multiple mechanisms. A complex interaction of counter-regulatory hormones including catecholamines, cytokines, glucagon, and cortisol leads to increased hepatic glucose production and insulin resistance. In addition, downregulation of GLUT transporters reduces glucose uptake in the peripheral tissues and contributes to hyperglycemia [3, 4]. A functioning postoperative stress response is necessary to an extent. In a cohort of patients undergoing cardiothoracic surgery, an inadequate stress response ($BG < 120$ mg/dL) was associated with increased mortality [5]. However, the stress response is often maladaptive, leading to uncontrolled hyperglycemia.

The harmful effects of hyperglycemia are well-studied and are mediated by a variety of mechanisms; catecholamine and cytokine release, endothelial dysfunction, platelet activation, electrolyte and fluid shifts, and immune dysregulation all play a role [3, 4, 6]. Hyperglycemia inhibits myocardial glycolysis and increases the metabolism of free fatty acids, resulting in a deficit of glycolysis-derived ATP that destabilizes cell membranes and can predispose to cardiac arrhythmias [7]. The disruption in lipid metabolism also leads to endothelial dysfunction and thrombogenesis [8]. Hyperglycemia causes the deregulation of noncoding microRNAs which regulate posttranscriptional gene expression mediating angiogenesis and oxidative repair, further exacerbating endothelial dysfunction [9]. Severe hyperglycemia can induce an osmotic diuresis which can result in hypovolemia and contribute to renal injury. Hyperglycemia has also been shown to impair leukocyte function, reduce collagen synthesis, and lead to poor wound healing and increased rates of infections [4, 10]. In addition, advanced glycosylation end products accumulate in the setting of hyperglycemia, activating the inflammatory cascade via nuclear factor κ B, activated protein-1, and the early growth response [4, 8, 11]. Increased cytokine release and endothelial dysfunction in response to hyperglycemia have been shown to stimulate a postoperative capillary leak syndrome which can lead to multiorgan failure [3, 12].

Hyperglycemia is an independent predictor of poor surgical outcomes including increased morbidity and mortality in patients with and without DM [13]. In a meta-analysis of 15 studies of non-DM patients, those with blood glucose concentrations >110 mg/dL had a 3.9-fold higher risk of death after myocardial infarction compared to those with lower glucose concentrations [14]. In fact, the harmful effects of stress hyperglycemia appear to be more pronounced in non-DM patients [15, 16]. In a study of 141,680 elderly patients hospitalized for acute myocardial infarction, hyperglycemia was associated with a 10–39% 30-day mortality in non-DM patients, compared to 16–24% in DM patients [17]. The presence of DM may foster adaptation to elevated glucose levels via downregulation of GLUT transporters and thus less hyperglycemia-related toxicity [18].

The harmful effects of hyperglycemia appear to be dose-dependent; longer duration and increased levels of hyperglycemia are both associated with increased

morbidity and mortality in patients undergoing CABG surgery [19]. The harmful effects of glycemic variability are also well documented. Intermittent hyperglycemia induces many of the same changes seen with prolonged hyperglycemia, including the production of reactive oxidative species, cellular apoptosis, immune system deregulation, and vascular injury [20–22]. A prospective study of 227 patients undergoing cardiac surgery demonstrated that patients who spent <80% of postoperative time within the target glycemic range (BG 108–146 mg/dL) had longer times on mechanical ventilation, longer intensive care unit (ICU) stays, and increased rates of wound infection [23]. Other studies have shown glycemic variability to be an independent predictor of increased mortality and poor outcomes in CABG surgery [24, 25].

Insulin administration lowers blood glucose and has independent advantageous effects on the inflammation and tissue injury caused by hyperglycemia. Insulin suppresses inflammatory cytokine release and the early growth response under normal conditions and has been shown to decrease the production of reactive oxidative species [8, 11]. Insulin also reduces endothelial injury via the production of nitric oxide and resultant vasodilatation [4, 26]. While hyperglycemia is associated with increased mortality in patients without DM compared to with DM, the former are significantly less likely to be treated with insulin [17], which suggests that treatment of hyperglycemia with insulin is effective at reducing the harmful clinical effects of hyperglycemia.

While hyperglycemia needs to be corrected, overzealous treatment is also associated with harm. Hypoglycemia activates the sympathetic nervous system, stimulating the release of glucagon and epinephrine which act to alter regional blood flow and induce metabolic changes to protect brain function while glucose is low. The effects of hypoglycemia are transitory in young and healthy patients and rarely lead to serious consequences. However, in patients with existing endothelial dysfunction, such as those likely to undergo CABG surgery, hypoglycemia can worsen existing damage. Hypoglycemia in critically ill patients is associated with hypertension, cardiac arrhythmias, myocardial infarction, stroke, seizures, loss of consciousness, and coma [27, 28]. It is important to note that the studies showing increased mortality with tight glycemic control often do not account for the toxic effects of increased glycemic variability and thus may overestimate the harms associated with tight glycemic control.

Historical Perspective and Relevant Literature

Traditionally, perioperative glycemic management focused on avoiding DKA and acute hypoglycemia. Less emphasis was placed on correcting hyperglycemia, which was considered an important stress response. Early treatments included the use of subcutaneous, intramuscular, and/or intravenous (IV) insulin, and protocols varied widely [29–32]. By the end of the twentieth century, IV insulin became the

treatment-of-choice for perioperative hyperglycemia, but there were no universally accepted guidelines for glycemic targets [33, 34].

The landmark Leuven Surgical Trial in 2001 was the first randomized controlled trial (RCT) evaluating glycemic control using IV insulin in critical illness. It included 1548 critically ill patients and compared tight glucose control (BG 80–110 mg/dL) to a more relaxed target (BG < 215 mg/dL). Patients who were treated with tight glucose control had significantly better outcomes; mortality was decreased by 34%, and there were significant decreases in bloodstream infections, acute renal failure requiring dialysis, blood transfusions, critical illness polyneuropathy, prolonged mechanical ventilation, and prolonged time in the ICU [35]. The survival benefit of tight glycemic control was most significant in non-DM patients (8.4% vs. 4.7%) compared to DM patients (5.8% vs. 4.0%). The Leuven Surgical Trial led to widespread adoption of tight glycemic control; however the results could not be consistently replicated. A study by the same group in 2006 demonstrated that tight glycemic control improved morbidity but not mortality among patients in the medical ICU [36].

The benefits of tight glycemic control were widely questioned following another landmark trial known as the Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial. The NICE-SUGAR trial compared 6104 patients randomly assigned either tight (80–108 mg/dL) or moderate glycemic control (<180 mg/dL) and demonstrated increased mortality and a 13-fold increase in hypoglycemia in the tight control group [37]. After the NICE-SUGAR study, practice shifted, and more moderate targets for glycemic control (BG 140–180 mg/dL) were widely adopted.

The NICE-SUGAR trial differed from the Leuven Surgical Trial in several important ways which help to explain the discrepancy in results. The Leuven trials were single center and much more standardized; they utilized specially trained nurses, infused insulin with accurate pumps and through dedicated central line lumens, measured blood glucose values using whole arterial blood, and optimized nutritional support. In contrast, NICE-SUGAR, a large, international and multi-center trial, reflected more typical clinical practice; staff had variable levels of training, blood glucose values were obtained using multiple different methods, and nutrition support was suboptimal. The differences suggest that safe targets for glycemic control may vary across different institutions and should be adjusted based on the resources and level of training available. When staff are properly trained, protocols are optimized, and adequate resources are available, lower blood glucose values may be more safely targeted [38].

Tight glycemic control may be more important to achieve in non-DM patients. Hyperglycemia is associated with increased perioperative morbidity and mortality in patients without DM compared to DM [15, 16]. In a retrospective multicenter cohort study of 44,964 critically ill patients, glycemic targets for patients were tested based on DM status. For DM patients, a strict target (BG 80–110 mg/dL) was associated with increased mortality compared to a moderate target (BG 110–180 mg/dL). For non-DM patients, in contrast, a strict target (BG 80–140 mg/dL) was associated with a decreased mortality rate compared to a higher target [39]. In another cohort of critically ill patients, tighter glycemic control was associated with

improved outcomes in patients with stress hyperglycemia but not in patients with diabetes [40]. These findings were again replicated in the GLUCO-CABG trial of 302 patients undergoing CABG surgery; in non-DM patients, tight glycemic control (BG 100–140 mg/dL) was associated with a lower complication rate compared to a moderate control (BG 141–180 mg/dL), but there was no difference in outcome for DM patients [41].

Multiple studies have demonstrated a relationship between diabetes and poor outcomes in the setting of CABG surgery. A retrospective study including 6033 patients undergoing CABG surgery demonstrated that insulin-dependent diabetes is associated with increased risk of acute renal failure, deep sternal wound infection, and prolonged postoperative stay [42]. Other studies have shown that DM patients undergoing CABG surgery have increased mortality, stroke, renal failure, sternal wound infection, and recurrent ischemia [43–45]. DM is associated with increased readmission rates following cardiac surgery, both for any cause and for heart-related issues [46, 47]. Poor outcomes with DM patients undergoing CABG surgery were previously thought to be inescapable, a consequence of multiple conditions comorbid with diabetes including chronic kidney disease, peripheral arterial disease, obesity, and hypertension. However, multiple studies have shown that hyperglycemia itself in the perioperative period is associated with increased morbidity and mortality in the setting of CABG surgery [48–50].

Several studies have attempted to determine perioperative glycemic targets for patients undergoing CABG surgery specifically. In the Leuven Surgical Trial referenced above, which showed a significant mortality benefit and improved outcomes with tight glucose control (BG 80–110 mg/dL) in the postoperative period, 62% of enrolled patients had undergone cardiac surgery [35]. A landmark randomized, controlled trial in 2003 included 3554 patients undergoing CABG surgery. Patients were treated with either IV insulin and strict (BG 100–150 mg/dL) or moderate (BG 150–200 mg/dL) targets or subcutaneous insulin with a moderate (BG 150–200 mg/dL) target in the postoperative period. Mortality was reduced by 57% in the patients treated with IV insulin, and IV insulin treatment eliminated the increased mortality after CABG surgery associated with diabetes [7]. Another study of 141 patients undergoing CABG surgery in 2004 demonstrated that tighter glycemic control (BG 125–200 mg/dL) with IV insulin beginning before anesthesia and continuing for 12 h after surgery was associated with decreased mortality, length of stay, need for vasopressors, recurrent ischemia, and wound infections compared to standard therapy with subcutaneous insulin [12].

More recent studies in CABG surgery patients have demonstrated that overly aggressive glycemic control provides no clinical benefit but is associated with significant harm. A 2011 study stratified 658 DM patients into groups receiving tight (BG \leq 126 mg/dL), moderate (BG 127–179 mg/dL), and liberal (BG \geq 180 mg/dL) glycemic control in the postoperative period. The moderate control group had the lowest mortality and a reduced risk of major complications [51]. A prospective cohort study of DM patients undergoing CABG surgery corroborated these results by demonstrating that moderate glycemic control (BG 120–180 mg/dL) beginning at the induction of anesthesia and continuing for 18 h postoperatively was

associated with lower incidence of hypoglycemia but no significant difference in clinical outcomes compared to tight (BG 90–120 mg/dL) control [52]. Multiple additional studies in CABG surgery patients have shown no difference in perioperative complications or mortality with strict (BG 90–120 mg/dL) compared to conventional (BG 120–180 mg/dL) glycemic targets [53, 54]. The evidence seems to support the findings of the NICE-SUGAR trial, suggesting that moderate perioperative glycemic targets are most appropriate in CABG surgery patients.

When looking specifically at intraoperative glycemic management, the evidence is less clear. In a retrospective, observational study of 409 patients, each 20 mg/dL increase in glucose concentration greater than 100 mg/dL during cardiac surgery was associated with a 34% increase in postoperative complications [55]. However, around the time this study was performed, most clinicians tolerated blood glucose levels up to 180 mg/dL during the postoperative period. A randomized, controlled trial of 400 patients undergoing cardiac surgery assigned patients to tight (BG 80–100 mg/dL) or liberal (BG < 200 mg/dL) groups for intraoperative glycemic control, and all received tight control during their postoperative course. The patients in the tight intraoperative control group had increased complications, including the risk of stroke, and there was no mortality benefit. In fact, all four deaths in the study were patients in the tight control group [56]. A 2021 study of 144 patients undergoing CABG surgery showed no difference in the incidence of surgical site infections with tight (BG 110–149 mg/dL) compared to conventional (BG 150–180 mg/dL) intraoperative glycemic control [57]. A meta-analysis of five randomized trials including 706 patients undergoing cardiac surgery found no mortality benefit of intensive insulin therapy compared to a conventional approach [58]. Adequate glycemic control during the postoperative period has an outsized effect on the outcomes of cardiac surgery patients, and the benefit of initiating strict glycemic control during the surgery itself appears to be relatively limited.

Management Strategies

Glycemic management for CABG should start during the preoperative planning stage in the outpatient setting (see Fig. 21.1). It should ideally be a collaborative effort involving a multidisciplinary team including endocrinologists, cardiothoracic surgeons, anesthesiologists, intensivists, pharmacists, and nurses. Each patient planned for CABG surgery should have their hemoglobin A1c (HbA1c) tested early in the planning stage, regardless of diabetes status [59]. This will establish a new diagnosis of diabetes for some patients; in one study 5.2% of patients undergoing CABG surgery were found to have previously undiagnosed DM [2]. In addition, HbA1c is an important predictor of postoperative hyperglycemia and high glucose variability after CABG surgery, and it can help guide medication management at discharge [59, 60]. It may be worth delaying elective surgery in those patients found to have uncontrolled diabetes ($\text{HbA1c} > 7\%$), since those with well-controlled

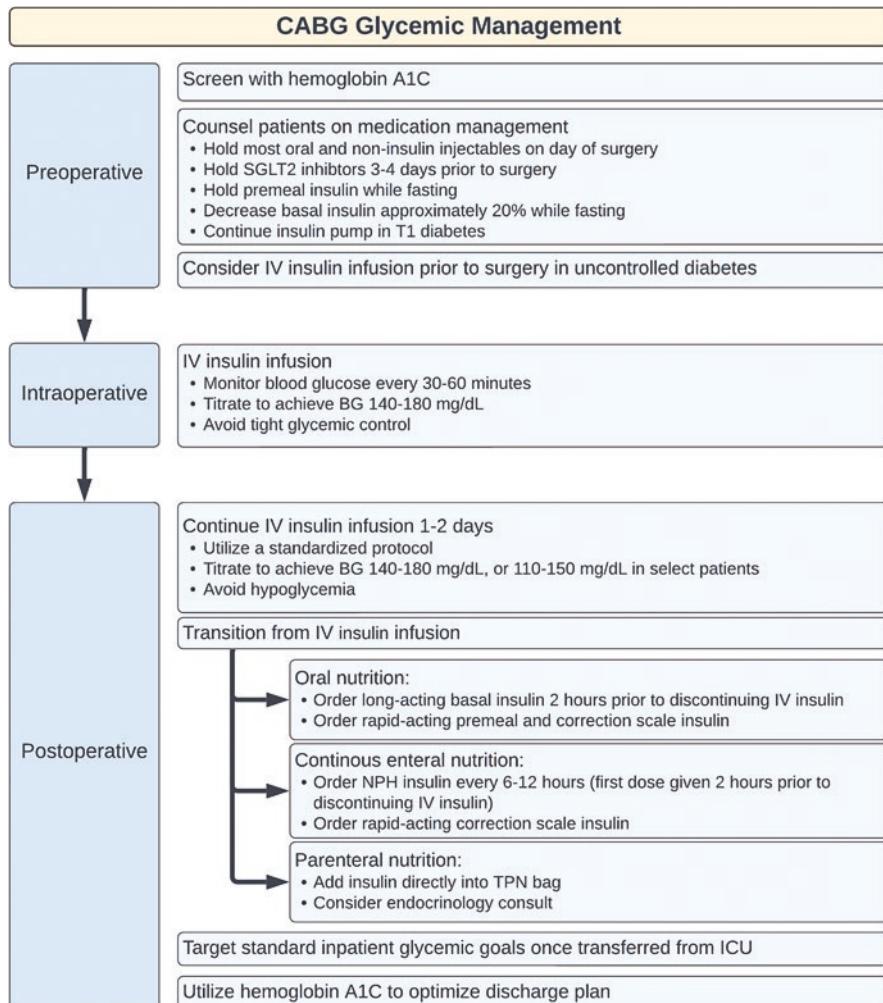


Fig. 21.1 Flowchart for suggested perioperative glycemic management in coronary artery bypass graft patients [59, 62, 63, 65, 73–77]

diabetes have similar outcomes compared to those without diabetes [61]. However, we recognize this is not often possible in the context of CABG surgery.

Patients with any history of DM should be counseled on the management of their medications prior to surgery, including insulin, non-insulin injectables, and oral agents. Most oral and non-insulin injectable medications should be stopped the morning of surgery, to prevent the risk of hypoglycemia while fasting [62, 63]. An important exception to this is the SGLT2 inhibitor medications, which have a known risk of diabetic ketoacidosis (DKA) with normal or slightly elevated blood glucose levels, known as euglycemic DKA. Euglycemic DKA can be precipitated by

surgery, and it has been reported following CABG surgery in patients taking SGLT2 inhibitors [64]. To minimize this risk, most SGLT2 inhibitors should be stopped at least 3 days prior and ertugliflozin at least 4 days prior to surgery [65]. Patients on insulin should be counseled to hold their pre-meal insulin while fasting. Basal insulin should be continued, or it can be decreased by approximately 20% to avoid hypoglycemia. Importantly, patients with type 1 diabetes always require basal insulin to prevent DKA. Patients with type 1 DM who utilize an insulin pump should continue to use the pump until just prior to surgery, when transitioned to an IV insulin infusion. An IV insulin infusion can also be started the day prior to surgery in patients with uncontrolled diabetes, to bring the blood glucose within target range.

During the intraoperative period, the Society of Thoracic Surgeons (STS) recommends IV insulin infusion be used in all patients [63]. Blood glucose should be monitored frequently, typically every 30–60 min, but possibly more frequently as needed. Insulin infusion rates should be titrated to achieve a moderate glycemic target (BG 140–180 mg/dL). We recommend against attempting to achieve tighter control (BG < 140 mg/dL) during surgery given the lack of evidence demonstrating a benefit and risk of hypoglycemia. The benefit of tight glycemic control warrants further investigation but should not be used routinely at this time.

Excellent glycemic management in the postoperative period is critical for achieving the best surgical outcomes. IV insulin should be continued postoperatively to allow for rapid titration. Glucose levels may fluctuate considerably due to stress from the surgery and various medications, some of which may be reconstituted in dextrose-containing fluid. Institutions should seek to adopt a standardized insulin infusion protocol, of which many are available [5, 7, 35, 66]. Blood glucose should be measured accurately; the gold standard is arterial whole blood. Point-of-care glucose monitors are convenient, but accuracy can be variable in critically ill patients and particularly in hypotensive patients [59, 67]. If point-of-care monitors are used, values should frequently be verified with more accurate methods. In addition, the use of continuous glucose monitors (CGM) has been proposed as an alternative method of glucose testing in both ICU and non-ICU patients with the goal of improving insulin titration and decreasing nursing workload, particularly during the COVID-19 pandemic. These studies generally demonstrate good accuracy and reliability of CGM use compared to POC glucose monitoring in cardiac surgery patients, with somewhat mixed results on whether they improve glycemic control in a clinically significant manner [68–72].

Blood glucose targets in the postoperative period are somewhat ambiguous given the multitude of sometimes-conflicting trials. The most effective targets may vary by institution and depend on the patient population, resources available, and level of training of the staff. The ADA and AACE recommend targeting a glucose range of 140–180 mg/dL for most critically ill patients [73, 74]. The STS recommends that all patients undergoing cardiac surgery be continued on an IV insulin infusion for at least 24 h postoperatively, to achieve a moderate glucose target (BG < 180 mg/dL) [63]. The Surgical Care Improvement Project (SCIP) is a quality initiative created by CMS and the Joint Commission with multiple performance measures including BG < 200 mg/dL during the first 2 postoperative days after cardiac surgery [75, 76].

In patients who require >3 days of ICU-level care postoperatively, a slightly stricter glucose target (BG 110–150 mg/dL) is advisable if it can be achieved safely. A similar target is also appropriate in patients without diabetes experiencing stress hyperglycemia. Low blood glucose (BG < 100 mg/dL) should be avoided in the postoperative period to avoid hypoglycemia [77]. Due to the complexity of glycemic control during the postoperative period, we strongly recommend a multidisciplinary approach involving endocrinologists, cardiothoracic surgeons, pharmacists, anesthesiologists, intensivists, and nurses.

IV insulin should be continued for at least 1–2 days following CABG surgery to allow postoperative stress levels to decrease. In addition, patients should be hemodynamically stable, off vasopressors, extubated, and ready to begin oral or enteral nutrition before IV insulin is discontinued. There are various ways to approach the transition process, and a standardized protocol to guide clinicians is essential. In the absence of a clear protocol, an endocrinology consultation may be helpful. Patients should be converted to subcutaneous basal-bolus insulin therapy, which is the standard of care in the inpatient setting. At our institution, the total daily subcutaneous dose is approximately 80% of the daily intravenous dose and is calculated using the total units administered intravenously over the past 6 h (see Fig. 21.2). 50% of the total daily subcutaneous dose is administered first as a basal dose, given 2 h prior to discontinuing IV insulin so that it may take effect. After IV insulin is discontinued, 50% of the total daily subcutaneous dose is administered before meals using a

| Total Daily Dose sq = 80% Total Daily Dose iv (Total insulin units administered intravenously in the last 6 hours / 6 hours) x 20 hours | | | |
|--|---|------------|--|
| Daily Nutritional Intake | Basal | Prandial | Supplemental |
| Eating > 50% of meals OR Receiving > 50% of total nutrition from enteral bolus feedings | 50% of TDD - Glargine Q24H - NPH (Q8 – 12H) | 50% of TDD | Correction scale TID with meals |
| Eating < 50% of meals OR Receiving < 50% of total nutrition from enteral bolus feedings OR Receiving continuous enteral feedings | 50% of TDD - Glargine Q24H - NPH (Q8 – 12H) | None | Correction scale TID with meals or q4h – q6h |

Fig. 21.2 North Shore University Hospital ICU protocol for transition from insulin infusion to subcutaneous insulin regimen. The first basal insulin dose should be administered 2 h prior to discontinuing insulin infusion. The prandial dose should be divided by 3 and administered TID with meals

rapid-acting insulin. Correction scale insulin is also administered before meals using a rapid-acting insulin. Premeal doses can be held or adjusted if patients are not eating or eating less, but correction scale insulin should still be continued. Those who are on continuous enteral nutrition may receive NPH insulin every 6–12 h in addition to rapid-acting correction scale insulin every 4–6 h. Those on parenteral nutrition should have insulin mixed directly into the parenteral nutrition bag with the guidance of a nutritionist or endocrinologist. In all cases, hypoglycemia should be avoided, and a standardized hypoglycemia protocol should be utilized.

Once patients are transferred out of the ICU to a lower level of care, standard inpatient glycemic goals should be targeted. For most hospitalized patients, a glucose range of 140–180 mg/dL is recommended, although more intensive targets (110–140 mg/dL or 100–180 mg/dL) may be appropriate if they can be achieved without significant hypoglycemia [73, 74, 78]. Blood glucose should be tested before meals and at bedtime in patients who are eating or every 4–6 h in patients who are NPO or receiving continuous enteral nutrition. Insulin dosing is highly patient-specific and should consider multiple factors including insulin requirements while in the ICU and personal history of diabetes. Those with no history of diabetes will likely require considerably less insulin once postoperative stress subsides and may require proactive lowering of insulin doses while blood glucose is in the target range. In contrast, those with a high A1c value or on high doses of insulin at home will likely continue to have high insulin requirements. Regardless, insulin doses should be titrated daily for all patients according to blood glucose trends.

The HbA1c value should be checked to differentiate between patients experiencing stress hyperglycemia from those with previously undiagnosed DM and to guide management at the time of discharge. Patients with stress hyperglycemia and no diabetes ($A1c < 5.7\%$) can usually be discharged home with no additional medications or follow-up. Patients with pre-diabetes ($A1c 5.7\text{--}6.4\%$) should be counseled on lifestyle modifications and instructed to follow up with their primary care doctor. Patients with newly diagnosed diabetes ($A1c \geq 6.5\%$) should be discharged with a clear plan for follow-up that includes diabetes education, nutritional counseling, and an eye exam. In addition, pharmacotherapy should be considered including glucose-lowering agents as well as ACE inhibitors or angiotensin receptor blockers and statins as per established guidelines. Patients with poorly controlled DM ($HbA1c > 7\%$) should have their medication regimen optimized, and patients with $HbA1c > 9\%$ should usually be discharged on insulin and/or GLP1 receptor agonist therapy [74]. Patients with type 1 diabetes should always be discharged on an insulin regimen. When considering the HbA1c, it is important to note that its use is limited in patients with hemoglobinopathies, recent blood transfusion, iron deficiency anemia, severe chronic liver or kidney disease, and various other conditions which affect hemoglobin structure or red blood cell lifespan [4].

It is increasingly important to consider newer antihyperglycemic agents, which have shown benefits including reductions in cardiovascular death, hospitalization for heart failure, stroke, and progression of CKD [79–83]. Adding SGLT2 inhibitors at the time of hospital discharge in patients with diabetes who are admitted to a cardiology unit has been shown to be safe and well-tolerated and results in a lower

rate of cardiovascular and any-cause death [84]. In addition, starting SGLT2 inhibitors at the time of discharge in patients with diabetes admitted for heart failure can decrease readmission for heart failure [85]. Adding GLP-1 receptor agonists at the time of hospital discharge in patients with uncontrolled diabetes has been shown to result in better glycemic control, increased weight loss, and less hypoglycemia compared with adding basal insulin [86]. Many patients who have undergone CABG surgery will have indications to start GLP-1 receptor agonists or SGLT2 inhibitors and, while not currently recommended for use in the hospital, these medications should be considered at discharge to improve long-term outcomes [74].

Conclusion

The association between perioperative hyperglycemia and poor surgical outcomes is well studied, and this remains true in the setting of CABG surgery. There is no clear consensus regarding the harms and benefits of tight glucose control, and optimal glycemic targets may depend on institution-specific factors including staff ratios, training, resources available, and nutrition support. While there may be no clear-cut targets for glycemic control, it is generally recommended to target a moderate blood glucose range (140–180 mg/dL) through the use of IV insulin infusion and subsequent transition to subcutaneous basal-bolus insulin.

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Chapter 22

Diabetes After Bariatric Surgery



Jenny C. Bello-Ramos, Ivania M. Rizo, and Sara M. Alexanian

Epidemiology

Obesity is defined by the World Health Organization (WHO) as abnormal or excessive fat accumulation that may impair health [1]. Body mass index (BMI) is a commonly used population-level measure to classify adults with obesity, which is defined as a BMI of $\geq 30 \text{ kg/m}^2$ or $\geq 27.5 \text{ kg/m}^2$ in persons of Asian descent [1, 2]. Obesity is associated with an increased risk of morbidity and mortality [3], primarily due to the common comorbidities of insulin resistance, diabetes, hypertension, cardiovascular disease, and lipid disorders [4, 5]. Over the past several decades, there has been an exponential increase in the incidence of obesity, with 1.9 billion people worldwide living with obesity as of 2016 [1]. In the United States, the prevalence of obesity in adults was 41.9% in 2020, and from 1999 to 2020, there was a dramatic increase in the prevalence of Class 3 obesity ($\text{BMI} \geq 40 \text{ kg/m}^2$) from 4.7% to 9.2% [6]. Among patients diagnosed with type 2 diabetes (T2DM), approximately 89.8% are overweight or have obesity [7].

Metabolic Surgery

One effective treatment option for obesity is bariatric surgery, which can promote significant and durable weight loss as well as substantially improve T2DM [8]. Bariatric surgery, especially in the context of T2DM, is commonly referred to as

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“metabolic” surgery, given the immediate impact of weight loss surgery on glucose homeostasis. For the purposes of this chapter, the term metabolic surgery will be used. The American Diabetes Association (ADA) recommends metabolic surgery as a treatment option for T2DM in adults with a BMI $\geq 35 \text{ kg/m}^2$ ($\geq 32.5 \text{ kg/m}^2$ in Asian Americans) who have not attained weight loss or improvement in comorbidities such as hyperglycemia with nonsurgical alternatives. Several randomized controlled trials have demonstrated that metabolic surgery is superior to conventional diabetes management in achieving glycemic targets and diabetes remission [9–16].

The two most common metabolic surgeries performed as of 2023 are the vertical sleeve gastrectomy (VSG) and the Roux-en-Y gastric bypass (RYGB). In the United States in 2020, there was an estimated 122,056 VSG and 41,280 RYBG performed [17]. The RYGB is performed by creating a small gastric pouch, usually less than 30 mL in size, and a gastrojejunostomy between the small pouch and the jejunum. Ingested food passes through the new small stomach pouch, bypassing the fundus and body of the stomach, the entire duodenum, and a portion of the jejunum. The residual nutrients are then absorbed in the remaining portion of the jejunum [18]. The VSG involves removal of approximately 75% of the stomach along a line roughly parallel to the greater curvature, resulting in a crescent-shaped stomach lacking most of the ghrelin-rich fundus. Additional bariatric and metabolic procedures include adjustable gastric banding (AGB), biliopancreatic diversion with duodenal switch, vertical banded gastroplasty (VBG), and one-anastomosis gastric bypass. The VBG is no longer performed, and use of AGB has diminished significantly over the past 10 years [19]. Selection of which bariatric procedure is most appropriate should be individualized based on goals of therapy including weight loss target and the presence of obesity-related comorbidities.

Short-Term Changes in Glucose Homeostasis

In the immediate postoperative period, there is substantial improvement in diabetes control in the setting of significant calorie reduction and improvement of insulin secretion and sensitivity [20]. Short-term studies have shown that very low-calorie diets and the acute changes after metabolic surgery result in similar glycemic improvement, demonstrating the importance of calorie restriction in the very rapid changes seen after surgery [21, 22]. Long-term improvement in glycemic control after metabolic surgery is due to weight loss-dependent and weight loss-independent mechanisms. Weight loss after metabolic surgery greatly contributes to insulin sensitivity and improvements in glucose homeostasis. Each bariatric procedure involves different gastrointestinal tract modifications; hence each procedure acts by means of different mechanisms to achieve T2DM resolution, including differential shifts in gastrointestinal hormone levels. Because of the gastrointestinal anatomic rearrangement, gut hormones are altered after surgery, leading to improvement in glycemic control. See Fig. 22.1 for changes after RYGB. Studies have shown that postprandial circulating glucagon-like peptide-1 (GLP-1) levels are markedly elevated after

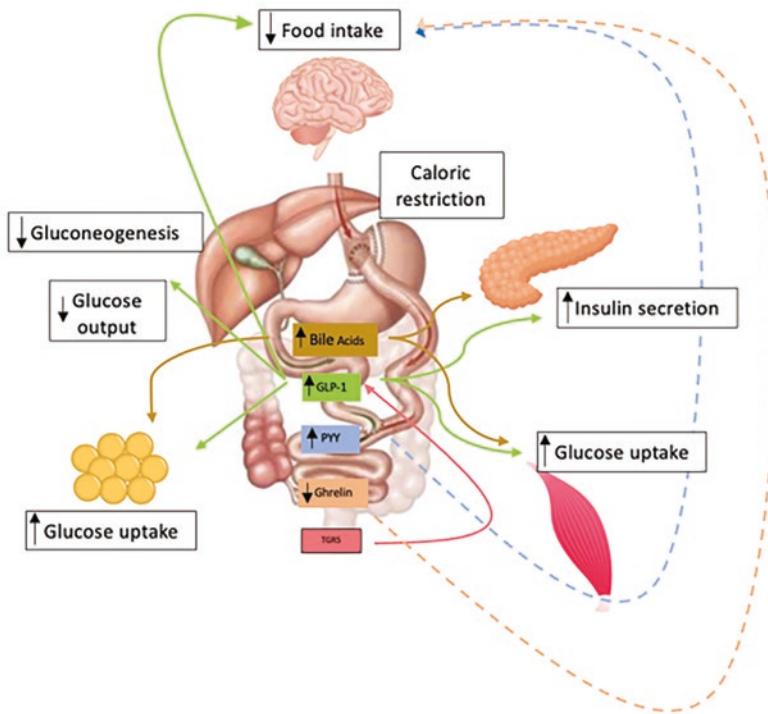


Fig. 22.1 Anatomic and hormonal changes affecting glucose homeostasis in the early postoperative period after Roux-en-Y gastric bypass [24, 25, 54–56]

metabolic surgery, in addition to elevated peak postprandial insulin levels [23, 24]. The robust increments in postprandial GLP-1 are present as early as postoperative day 2. Following both RYGB and SG, levels of bile acids increase significantly. The increase in bile acids is correlated with an increase in GLP-1 levels and a decrease in post-prandial blood glucose (25). Bile acids acting via TGR5 transcription pathway stimulate L-cell secretion of GLP-1 and PYY. Other hormones contributing to improvement of glycemic control within the first weeks of surgery include a decrease in circulating levels of ghrelin, which leads to reduced appetite and alterations in taste [24, 26].

Long-Term Diabetes Remission After Bariatric Surgery

Multiple studies have reported remission of T2DM after metabolic surgery, defined as a hemoglobin A1C (HbA1c) level of <6.5% measured at least 3 months after cessation of glucose-lowering pharmacotherapy [28]. No difference in terms of remission has been evidenced between RYGB and VSG at 5 years (45). Recent data

suggest greater remission rates of T2DM after RYGB vs VSG at 1 year (RR- 1.2; 95% CI, 1.00–1.45) with no difference found at 2–5 years [29]. Despite data that shows that a significant percentage of patients have recurrence of diabetes over time, a large proportion of those who undergo metabolic surgery maintain substantial improvements in glycemia from baseline to 5–15 years [30].

Perioperative Management

Prior to metabolic surgery, patients undergo a comprehensive multidisciplinary evaluation to determine suitability and optimize medical comorbidities. In terms of preoperative glucose control, there are currently no prospective randomized controlled trials that have evaluated the effects of different, and therefore optimal, pre-operative HbA1c levels. The 2019 recommendations from the American Society for Metabolic and Bariatric Surgery (ASMBS) suggest an HbA1C target of 6.5–7% and periprocedural blood glucose levels of 80–180 mg/dL [31]. More liberal targets including an HbA1c range of 7–8% may be appropriate in patients with advanced complications, extensive comorbidities, or long-standing diabetes. Clinical judgment should be used in determining whether to proceed to surgery in patients with an HbA1c >8% [32]. As with all planned surgeries, patients should receive counseling on how to adjust outpatient medications prior to the procedure, and these same recommendations are also appropriate for patients undergoing metabolic surgery. See Chap. 19 for more information.

Perioperative hyperglycemia in individuals with diabetes has been identified as a risk factor for poor clinical outcomes after cardiac and non-cardiac surgery [33, 34]. The stress of surgery and effects of anesthesia alter the balance between hepatic glucose production and utilization in peripheral tissues, leading to insulin resistance during the immediate post-operative course [35]. The Endocrine Society currently recommends intraoperative blood glucose (BG) levels below 180 mg/dL [36]. This can be achieved via use of either a continuous intravenous insulin infusion or intermittent doses of rapid- or short-acting subcutaneous insulin. The appropriate choice will depend upon the duration of surgery, invasiveness of the procedure, anesthetic technique, and the expected time to resume oral intake [37].

Few studies have focused on the glycemic management in hospitalized patients specifically after metabolic surgery. Datta et al. evaluated whether once-daily long-acting insulin as insulin glargine or regular sliding scale insulin (SSI) could provide better glycemic control after metabolic surgery [38]. In this single-center trial, 81 patients both with and without diabetes who had a BG of >144 mg/dL after surgery were randomized to receive long-acting insulin (at 20 times the last unit/h insulin infusion rate or at 0.3 unit/kg subcutaneously every 24 h) versus SSI. In this study, the long-acting insulin group had more glucose readings at goal (80–140 mg/dL) with lower rates of hyperglycemia and no difference in hypoglycemic events, length of stay, or postoperative infection rate [38]. For those patients transitioned from the insulin infusion, the mean weight-based glargine dose was 0.4 units/kg/day. While

mean doses were not provided for each postoperative day, patients in the basal insulin group received a mean total dose of 179 ± 108 units of insulin during the entire hospital stay, while patients randomized to SSI received an average of 44 ± 42 units. The average hospital stay was 3.7 ± 1.7 days. There were three episodes of hypoglycemia, two in the glargin group and one in the SSI group.

Blackstone et al. published a retrospective longitudinal analysis of patients after metabolic surgery who received either intermittent short-acting insulin every 6 h versus continuous insulin infusion therapy begun preoperatively and continued for 24 h. Those in the insulin infusion arm had a target glucose of 80–120 mg/dL and received an average of 138 units of insulin during the 24 h of therapy (patients on average weighed 140 kg, therefore received nearly 1 unit/kg over 24 h). Most patients (92%) underwent RYGB [39].

Wirunsawanya et al. in a single center retrospective cohort study compared glycemic management strategies in 160 patients after metabolic surgery [40]. The aim of the study was to determine what proportion of patients required basal insulin to control BG after surgery and what doses were generally required. Patients with HbA1C <7% prior to surgery who were taking no medications preoperatively or metformin monotherapy were excluded from the study as they were considered unlikely to require insulin during the inpatient stay. The analysis showed that 49% of patients received basal insulin plus SSI for glycemic control; 48% were on SSI alone; 2% were on basal insulin, prandial, and SSI; and 1 patient (0.6%) was prescribed prandial insulin and SSI alone. Patients selected to receive only SSI had lower mean BG values compared with those receiving basal insulin plus SSI. Postoperative basal insulin requirements progressively declined from postoperative day (POD) 0 to POD 2 with a median total daily dose of 36 units/day down to 5 units/day prior to discharge. This initial dose was equivalent to an average of 0.23 units/kg/day of basal insulin, similar to doses recommended for other hospitalized patients with hyperglycemia. Patients with poor and moderate glycemic control (HbA1C $\geq 8\%$) preoperatively were more often treated with basal insulin plus SSI, whereas most patients with good control prior to surgery could often be treated with SSI alone [40].

Additionally, in another single-center retrospective study, inpatient insulin doses were reviewed in 114 patients with T2DM who underwent RYGB and were using insulin preoperatively [41]. Patients who received glucocorticoid therapy perioperatively were excluded. By POD 2, there was an 87% median reduction in the total daily insulin dose compared to pre-surgical doses [41]. In this cohort study, the median preoperative total daily insulin dose was 75 units (0.58 unit/kg). On the day of surgery, the median total daily insulin dose was 8 units (0.03 unit/kg), which continued to decrease on POD 2 to a median of 6 units (0.04 unit/kg). At POD 0, 11.4% of patients were on basal/bolus insulin, while on POD 1, 21.9% of patients were on basal/bolus insulin. At POD 2, 19% of the patients were on a basal-bolus insulin regimen, and 81% were treated with SSI alone. The weight-based percentage of the basal dose and specific basal/bolus doses were not reported.

Other inpatient insulin regimens have been suggested as part of guidelines and based on clinical experience. The ASMBS recommends adjusting insulin to reduce

the risk of hypoglycemia and using long-acting basal insulin and rapid-acting analog insulins before meals to control BG [19]. Rometo et al. describe using a dose of 0.1 units/kg of basal insulin for patients with a BG of >180 mg/dL after surgery [42]. As with all hospitalized patients, oral medications are generally discontinued in favor of insulin in the acute setting, though some centers may reintroduce metformin prior to discharge [43].

The studies and recommendations mentioned above describe a wide range of insulin dosing in the immediate postoperative period. Of note, studies showing higher dosage of insulin had more aggressive BG targets, and studies with lower doses overall appear to have reported higher average BG levels postoperatively, though direct comparisons are not possible as BG levels were not reported using the same metrics between studies. Additionally, earlier studies were more likely to have patients receive IV insulin in the postoperative period, and patients may have had an open abdominal procedure which could potentially increase stress and postoperative insulin needs. Therefore due to differences in the types of studies, BG targets, and demographic data available in the literature, there is a lack of data to support a specific dose of insulin that is appropriate for all patients in the immediate perioperative time period after metabolic surgery.

Given the rapid improvement in glucose control in the immediate postoperative period, the main glycemic management decision in the immediate postoperative period is whether to start a long-acting basal insulin in addition to the SSI that will be used to monitor and correct hyperglycemia. Those patients preoperatively who are on high doses of insulin, present with significantly elevated BG, and have chronically poorly controlled diabetes are more likely to require basal insulin to maintain glucose levels at target. Based on the data mentioned above, a dose of 0.2–0.3 units/kg of basal insulin may initially be appropriate. However, this determination should be modified based on patient-specific factors, including preoperative basal insulin dose, renal function, age, and if the patient received glucocorticoids perioperatively. For patients with well-controlled diabetes on one or two non-insulin medications prior to surgery, monitoring with SSI is often an appropriate first step and all that is required to maintain glucose in the desired range. For patients who receive basal insulin, BG should be monitored carefully with a consideration to significantly decrease the dose if BG levels are improving, in particular on POD 2 and beyond.

After metabolic surgery, a reduction in the volume of the stomach and/or the creation of a small gastric pouch substantially limits the ingestion of solid food and proteins [44]. A low-sugar, clear liquid diet is usually initiated within 24 h of surgery and then is gradually changed to introduce food consistency, moving from clear liquids to soft and then to solids over a period of 2–4 weeks [44, 45]. Fluids and caloric intake are usually reduced to about 500 calories per day during this period, and the glycemic peaks after meals are generally considerably lower [46]. Due to the significant caloric restriction, consumption of small quantities of carbohydrates at a time, and the hormonal changes that occur after surgery, postprandial hyperglycemia is substantially decreased, and prandial insulin is infrequently required as noted in the above studies.

Discharge to Home

While patients can expect a significant improvement in glycemic control after discharge from the hospital, the time course and extent of improvement is variable, and there is limited data looking at the outcomes of medication adjustments in the immediate postoperative period after discharge. The determination of which medications to continue should be based on glycemic trends inpatient, preoperative diabetes history and control, and the risks and benefits of the individual medications [32]. Recommendations for adjustments in glucose-lowering medications at the time of discharge after metabolic surgery are summarized in Table 22.1.

For patients treated with non-insulin agents prior to surgery who have postoperative euglycemia or only mild hyperglycemia, antihyperglycemic therapy can usually be discontinued with monitoring of fasting and postprandial glucose after discharge [45].

Metformin can be safely resumed, if needed, on the third day after surgery if no other contraindication exists. Gastrointestinal discomfort is a common side effect of metformin and is also commonly seen in patients after metabolic surgery; therefore

Table 22.1 Recommendations for glucose-lowering medications at the time of hospital discharge after metabolic surgery [57]

| Hypoglycemic agents | Recommendations |
|---|---|
| Biguanides | Can resume at the time of discharge if there are no concerns for side effects or contraindication. Extended release formulations must be changed to immediate release or liquid formulations, while pills must be crushed |
| Sulfonylureas and meglitinides | Do not resume at the time of discharge |
| Thiazolidinediones | Do not resume at the time of discharge |
| DPP-4 inhibitors | Can resume at the time of discharge |
| GLP-1 receptor agonist/dual-acting GLP-1 and glucose-dependent insulinotropic polypeptide [GIP] receptor agonists | Unclear benefit immediately after surgery. Consider temporary discontinuation until food intake stabilized and need for further glycemic lowering has been determined |
| SGLT-2 inhibitors | Withhold SGLT2 inhibitors during the first weeks following bariatric surgery due to acute calorie restriction. Can consider restarting treatment later once tolerating good oral intake, particularly in individuals who could benefit from their cardiovascular and renal protective effects |
| Alpha-glucosidase inhibitors | Do not resume at the time of discharge |
| Long-acting insulin | Can be stopped in many patients upon discharge. For patients who require insulin on discharge, dose determination should be based on patient-specific factors, including perioperative basal insulin dose, renal function, age. Consider 0.1 units/kg as starting point |
| Short-acting insulin, mixed insulins | Do not resume at the time of discharge |

it is not recommended to be given during the immediate recovery period. The biological availability of metformin increases by 50% after gastric bypass; therefore the prescribed dose should be reduced [45]. Patients taking the extended-release form of metformin prior to surgery will need to be changed to a liquid form or the immediate release formulation until they no longer need to ingest only crushed pills. Due to the increased risk of hypoglycemia and weight gain, it is recommended that patients using sulfonylurea medications discontinue them upon discharge.

GLP-1 receptor agonists promote weight loss through multiple signaling mechanisms, and the use of these drugs is recommended as an option for long-term glycemic control and weight loss promotion after surgery [47, 48]. Similarly, dipeptidyl peptidase 4 (DPP-4) inhibitors are weight neutral and can be a good option for glycemic control. Gastrointestinal side effects are relatively common during treatment with GLP-1 receptor agonists; therefore they should be avoided in the early postoperative course when oral intake is low. There is little data examining the utility of incretin-based therapies in the immediate postoperative period after metabolic surgery, and patients can be individually assessed to determine the necessity of continuing these classes of medication upon discharge. The ASMBs suggests continuing metformin and/or incretin therapies at discharge until clinical resolution of diabetes has been demonstrated [31].

It is generally recommended not to resume sodium-glucose cotransporter-2 (SGLT-2) inhibitors after metabolic surgery [31]. The decision to resume this class of medication at the time of discharge is now more complicated by the fact that SGLT-2 inhibitors are increasingly used to treat not only T2DM but also cardiovascular disease, heart failure (HF), and chronic kidney disease (CKD). SGLT-2 inhibitors have demonstrated a benefit in reduction in major adverse cardiovascular events, preservation of renal function in CKD, and a reduction in hospitalizations in patients with T2DM and HF, in particular for patients at high risk for these complications [49]. However SGLT-2 inhibitors have been reported to increase the risk of diabetic ketoacidosis (DKA), and this can occur perioperatively and in the setting of significant reduction in food intake anticipated after the surgery [50, 51]. When SGLT-2 inhibitors have been used as a medication preoperatively for glycemic control, it is prudent to discontinue them upon discharge after metabolic surgery. For patients using these medications for heart failure or other indications, a discussion with the patients' cardiologist or other relevant specialist is advisable to determine the appropriate course, but resumption would be best postponed until the patient is tolerating good oral intake to mitigate the risk of DKA.

For those patients using insulin prior to surgery, doses should be reduced at the time of discharge, and patients may no longer require insulin therapy. For patients who were taking large doses of insulin with poor diabetes control preoperatively and who have a significant insulin requirement during the postoperative hospital course, discharge on a low dose of basal insulin can be considered. When determining if a patient requires insulin on discharge, it is also important to carefully review the patient's diabetes history. Patients with type 1 diabetes or insulin deficiency may undergo metabolic surgery; therefore providers should carefully ascertain the type of diabetes before stopping all insulin therapy during the hospital stay and at

discharge. If there is doubt as to the safety of stopping insulin, it may be reasonable to check a C-peptide level prior to surgery [52].

There is limited data to inform practice as to appropriate insulin dosing at discharge in patients for whom it is needed. Fenske et al. sequentially compared a non-standardized diabetes management protocol with a standardized protocol upon discharge in patients with T2DM after RYGB [53]. Fifty patients in the standardized protocol were prescribed metformin 1 gram twice per day if no contraindication existed as well as basal insulin glargine with a dose equivalent to the patients' total insulin requirement for the 24 h prior to discharge. Patients contacted providers daily via text message to assist in insulin titration until BG levels were stable and at target of 100–120 mg/dL fasting. All patients showed a reduction in insulin need during the first postoperative week, and 2 weeks after surgery, the mean insulin dosage was reduced by 68% from 50 to 16 units/day. Compared with the non-standardized group, this group had a greater percentage of subjects (50% vs 6%) who achieve diabetes remission at 1 year.

Wirunsawanya et al. reviewed data for patients with hyperglycemia still requiring insulin at the time of discharge after metabolic surgery at their institution and found that for patients discharged on 0.1 units/kg/day of basal insulin and seen at 2-week follow-up, there were no noted hypoglycemic events. Data was obtained by chart review retrospectively. About 30% of patients had insulin doses further reduced at the time of 2-week follow-up, and only a small number of patients required insulin dose increases [40].

Patients with T2DM should not generally be discharged on standing prandial insulin due to the very small frequent meals consumed in the immediate postoperative period. Patients who used a mixed insulin prior to surgery should be changed to a basal formulation if insulin is needed at the time of discharge. For any patient discharged on insulin, it is recommended they closely monitor BG at home. Patients should receive instructions on how to mitigate the risk of hypoglycemia and to anticipate further reduction in insulin needs. It may be advisable to have the patient reduce the dose by 50% or stop the basal insulin if the patient experiences BG less than 100 mg/dL. Patients should be given instructions to call their outpatient provider for persistent high BG or hypoglycemia, and those discharged on insulin should have close follow-up.

Patients who present for metabolic surgery with very poorly controlled diabetes and have significant insulin requirements during the hospital stay who were not using insulin preoperatively present a challenge at the time of discharge. Fortunately, the rapid improvement in glycemic control in the weeks following surgery limits the likelihood of prolonged hyperglycemia. Given that insulin sensitivity and insulin needs change rapidly after surgery and that insulin is a high-risk medication, it is generally not advisable to discharge such patients as newly started on insulin therapy.

Summary

The prevalence of obesity and T2DM continues to rise, and metabolic surgery remains one of the most effective treatment options to achieve glucose control and diabetes remission. Patients can expect significant improvement in glycemic control with a reduction in the burden of diabetes medication after surgery. Providers need to balance the needs of perioperative glycemic control with the significant and rapid changes that occur postoperatively when determining the appropriate treatment both during the hospital stay and at the time of discharge. Further research needs to be done to examine optimal insulin and medication management for these patients and to guide medication adjustments at the time of discharge.

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Chapter 23

Inpatient Management of Patients with Diabetes and Kidney Disease



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Introduction

Diabetic nephropathy is the most common cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD); half of patients on dialysis worldwide have diabetes [1]. The prevalence of CKD among people with diabetes is estimated at 40% [2]. While several recent reports show a trend of reduced ESRD in patients with type 1 diabetes mellitus (T1DM), attributed to increased surveillance, glycemic control, and RAAS blockade with angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists, the overall incidence of nephropathy continues to rise due to increasing rates of type 2 diabetes mellitus (T2DM), posing a significant burden on patients and healthcare systems [54].

Even seemingly transient episodes of acute renal injury can portend worse outcomes. In an observational study of patients with diabetes, 29% of those admitted to the hospital experienced one episode of acute kidney injury, which increased their risk of progression to ESRD [3]. This underscores the importance of close follow-up of hospitalized diabetes mellitus (DM) patients and dose adjustments for their anti-hyperglycemia therapy as declining glomerular filtration rate (GFR) on a prior regimen may lead to hypoglycemia. Hyperglycemia and hypoglycemia are independent risk factors for inpatient outcomes. Hospitalized patients with renal disease are at high risk of hypoglycemia, due to fluctuations in kidney function, oral intake, medications, and other factors related to their illness. A US Veterans Affairs study found that when serum creatinine increased from 50% of baseline, risk of hypoglycemia after discharge increased by 27% [4]. Therefore the spectrum of illness encountered requires knowledge about medication adjustments for renal function

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and use of diabetes technology such as continuous glucose monitors to maintain glucose targets and minimize complications.

Insulin has long been the gold standard for diabetes therapy in the hospital, but more recently newer diabetes drugs that are safe and effective in compromised renal function have been evaluated. Their use is becoming increasingly more common as multiple trials have demonstrated their efficacy. DPP-4 inhibitors, namely, sitagliptin and linagliptin, have been studied in the management of diabetes patients in the hospital and nursing home setting and in the transition from hospital to home. Data on the use of SGLT-2 inhibitors in the hospital is emerging with trials evaluating their initiation for heart failure (HF) outcomes when started soon after admission or just before or after discharge [5]. The safety of these drugs in HF trials can be extrapolated for glucose control. GLP-1RAs and SGLT-2 inhibitors have also been shown to reduce progression of renal disease with appropriate dose adjustments for the CKD population. The use of insulin in the hospital is a risk factor for hypoglycemia. Studies of hospitalized patients with CKD have highlighted the importance of dose adjustment with level of CKD to prevent hypoglycemia [6–8].

This chapter focuses on the importance of considering renal function in managing inpatient diabetes. It aims to provide a comprehensive review of insulin dosing in renal insufficiency including in those on peritoneal and hemodialysis, review the use of newer non-insulin agents in inpatient diabetes, discuss the use of technology such as continuous glucose monitors in the inpatient setting, and explain treatment modifications for DKA in patients with ESRD.

Pathophysiology

The pathophysiology of insulin and glucose metabolism in chronic kidney disease is complex based on where insulin enters the circulation. Endogenous insulin is secreted systemically via the portal vein, with the liver being the primary site for metabolism via first pass. The kidney has a secondary role in the metabolism of endogenous insulin and clears approximately 65% of insulin that reaches it. In contrast, exogenous insulin is primarily renally cleared as it bypasses the liver and directly enters the systemic circulation. Renal function directly affects the metabolism of exogenous insulin, and its clearance is reduced with renal insufficiency and most significantly when GFR drops to 15–20 mL/min.

In early CKD, hyperglycemia may occur due to the decreased insulin secretion from beta cells and increased insulin resistance in fat and skeletal muscle. Insulin resistance is partly due to multiple shared risk factors for developing renal disease such as diet, obesity, and sedentary lifestyle. Some unique attributes in CKD that promote insulin resistance include uremic toxins, vitamin D deficiency, and metabolic acidosis [5].

In contrast, hypoglycemia, especially while fasting, is a common complication in ESRD with and without intermittent HD even in patients without diabetes. This hypoglycemia is multifactorial due to decreased insulin clearance, reduced hepatic

and renal gluconeogenesis, inadequate nutrition, hypoglycemia unawareness, glucose loss to dialysate, and diffusion of glucose into erythrocytes during dialysis. In patients with moderate levels of beta cell function, the glucose content in dialysate may stimulate insulin secretion and can lead to hypoglycemia following dialysis. In contrast, patients with reduced or absent beta cell function are at higher risk of developing hyperglycemia several hours following dialysis due to increased insulin resistance, absorption of insulin by dialyzers, and secretion of counterregulatory hormones in response to dialysis-induced hypoglycemia [9].

Challenges in Management

Blood glucose targets need to constantly be adjusted in patients with renal insufficiency. Poorly controlled DM increases mortality while advancing renal dysfunction increases the risk of hypoglycemia. A Canadian study of over 23,000 patients with estimated GFR less than 60 mL/min identified a U-shaped mortality curve with HbA1c <6.5% or >8.0% [10], suggesting a BG goal between these values may be ideal. The 2022 consensus report between the American Diabetes Association and Kidney Disease Improving Global Outcomes (KDIGO) concurs with a HbA1c target between 6.5 and 8% to improve survival and reduce microvascular and macrovascular complications. A goal HbA1c of 6.5% versus 8% should be individualized based on key clinical characteristics such as age and comorbidities [11].

There are several ways to monitor long-term glycemic control; unfortunately all these methods are fraught with problems after Stage 3 (GFR 30–59 mL/min) renal disease.

HbA1c, the most common diagnostic test for assessing long-term (3 month) glucose control, is less reliable in renal failure. Several factors in CKD affect hemoglobin glycation rates, and furthermore, patients commonly have anemia, receive erythropoietin and blood transfusions, and have shortened red blood cell lifespan due to uremia, all of which directly affect the veracity of the HbA1c value. For these reasons, patients with advanced CKD tend to have falsely low HbA1c values that are often not true indicators of their glycemic control.

Fructosamine is a general measure of glycated serum protein and measures glycemic control over a 2- to 3-week period. Fructosamine is not influenced by anemia or variant hemoglobin complexes, but rather is influenced by serum protein concentrations as well as low molecular weight compounds in the plasma, such as albumin, bilirubin, and uric acid. It may be falsely low in low-protein states including nephrotic syndrome or liver disease. Conversely, it may increase in states of higher protein turnover, such as dialysis [12].

Glycated albumin may be a more accurate measurement of glycemic control in patients with renal disease [13]. However, there are still limitations for the use of glycated albumin because data on therapeutic targets is minimal and variability exists in high albumin turnover states, such as patients with proteinuria or on peritoneal dialysis.

For hospitalized patients, point of care (POC) glucose testing is the currently employed method for following glucose levels. Anemia, hypotension resulting in hypoperfusion, and low pH (<6.95) in critically ill patients can all lead to low POC results. In contrast, polycythemia and high pH may lead to falsely elevated glucose recordings. Meanwhile serum glucoses are generally accurate, and POC glucose testing can be compared to serum values to gauge accuracy of POC testing.

Inpatient Continuous Glucose Monitoring

Due to the above shortcomings, continuous glucose monitoring (CGM) has a potential advantage in evaluating glycemic control in chronic renal disease and has been shown to improve glucose control in this population [14]. CGMs both real-time (rt-CGM) and intermittent/flash (is CGM) CGM measure interstitial glucose every 1–5 min, and each device lasts for 10 or 14 days and implantable devices up to 6 months. A continuous stream of data helps identify glucose patterns with daily graphical representation of trends which assists in medication adjustment. For bolus insulin dosing, current practice requires POC testing in most hospitals despite the presence of a CGM. A hybrid approach with intermittent POC validation of CGM helps reduce the POC burden. In outpatient settings, sensors guide nutritional therapy and physical activity and can similarly be used in the hospital especially around vulnerable periods like post-dialysis when there can be significant excursions. The major benefit of CGMs includes their ability to determine the rate of change of glucose and warn of hypo- and hyperglycemia via predictive algorithms by means of arrows and alarms.

The accuracy of CGM in advanced CKD with rt-CGMs is found to be reasonable, while intermittent CGM use is reported to have a higher mean relative average difference (MARD), especially during periods of fluid shift and rapid glucose excursions [15, 16]. Different sensor technologies report varied interferences with acetaminophen, aspirin, hydroxyurea, and tetracycline but specify no ESRD-related interfering factors. Current hospital use of CGM is under Emergency Use Authorization for the COVID pandemic. There remain considerable limitations to the use of CGM in the hospital including their cost, need for significant resources for implementation, requirement for their removal for several radiological procedures, need for diabetes technology expertise in the hospital, and their integration with the electronic medical record.

Lastly, technology integration of sensors with augmented closed loop insulin pump therapy was evaluated in hospitalized T2DM requiring dialysis and improved mean sensor glucose and time in range (TIR) without increasing hypoglycemia [17]. The clinical benefit of CGMs in the CKD population is evident and their potential to improve TIR [18]. Larger multicenter studies evaluating the accuracy and efficacy of newer-generation sensors in the inpatient setting especially around hemodialysis and peritoneal dialysis are needed.

Diabetes Medications

Insulin Therapy

Insulin therapy is currently recommended as standard practice for the treatment of hyperglycemia in the hospital setting. In contrast to endogenous insulin, exogenous insulin does not undergo first-pass metabolism in the liver; therefore with renal impairment, the clearance of insulin is progressively impaired, and it may be necessary to adjust insulin regimens to minimize hypoglycemia. Overall, the reduction in insulin requirements is similar between patients with type 1 and type 2 diabetes irrespective of residual beta cell function [19].

CKD Stage 1 and 2 (eGFR >60 mL/min)

Adjustment in insulin doses for patients with eGFR greater than 60 mL/min is needed only for dietary restrictions or NPO status. Assuming that the patient was well controlled prior to admission, suggested dose reductions are 25–30% of total daily dose for NPO patients on basal-bolus insulin and 50% for basal-only regimens [8, 20]. A more conservative reduction may be more appropriate in those with overt hyperglycemia.

CKD Stages 3/4 (eGFR 15–59 mL/min)

For insulin-naïve patients with an eGFR less than 60 mL/min, a starting total daily insulin dose of 0.2–0.3 units/kg/day is recommended according to the Endocrine Society standards of care [21]. This recommendation is in line with a study that found that patients treated with a total daily dose of insulin of 0.25 units/kg/day had equivalent control of hyperglycemia with half as many subjects experiencing hypoglycemia when compared to patients receiving 0.5 units/kg/day [6]. In patients on insulin prior to admission with an eGFR <50 mL/min, a total daily insulin reduction of 25–50% is reasonable [8] divided as 50% basal with the remaining 50% should be divided by three prandial insulin doses with each meal. There should be a low threshold to hold prandial insulin for NPO and dose reductions with poor appetite, dietary restrictions, or pending procedures. Postprandial meal injections (or mid-meal after 50% of the meal is consumed) should be considered for patients with unpredictable intake (e.g., post-surgery and gastroparesis). Patients with low but stable renal function, adequate glucose control, and minimal hypoglycemia may not require major changes to their insulin regimen while hospitalized.

CKD Stage 5/ESRD (eGFR <15 mL/min)

Once patients begin to receive dialysis, peripheral insulin resistance improves resulting in decreased insulin requirements by 40–50%. Many patients with advanced renal failure have delayed gastric emptying, and moving prandial rapid-acting insulin doses from before meals to after meals may better align with both peak insulin activity and blood glucose levels [22].

Hemodialysis

The unpredictable timing of hemodialysis and variability in dietary status in hospitalized patients make communication between treatment teams and timely adjustments to insulin regimens essential to minimize the risk of hypoglycemia. Long-acting insulins such as glargine, detemir, and degludec are all recommended in patients on hemodialysis. Patients switched from twice-daily NPH insulin or pre-mixed insulin to once-daily glargine were shown to have an improvement in HbA1C and a 96% reduction in hypoglycemic episodes [23]. Other studies on timing of long-acting insulin have shown that glargine injections during and post-hemodialysis resulted in improvements in HbA1C and BG levels [24, 25]. Based on the results of a study that showed a decreased basal insulin requirement in patients on hemodialysis, a 50% reduction in glargine for patients admitted to the hospital requiring acute dialysis is reasonable [26]. Detemir and degludec have been shown to be safe in varying degrees of renal dysfunction including ESRD [27, 28].

Rapid-acting (RA) insulin analogues such as aspart, lispro, or glulisine are preferred for prandial insulin requirements over regular insulin as they reach peak concentrations rapidly, have a shorter duration of action, and are metabolized faster than regular insulin resulting in fewer hypoglycemic episodes in patients on hemodialysis [29]. One study found that BG levels in hemodialysis patients reached a nadir 3 h after lispro injection, while BG levels continued to decline 4 h after injection of regular insulin increasing the risk of hypoglycemia [29]. Studies have shown that the dosages of RA insulins were lower in patients with renal impairment by 30–40% in glulisine and 33% in lispro and therefore appropriate dose reductions can prevent hypoglycemia [30].

Current use of lower glucose-containing dialysate (100 mg/dL vs 200 mg/dL) mitigates dialysis-associated hypoglycemia and avoids significant post-hemodialysis hyperglycemia [31]. In the inpatient setting, hypoglycemia is more common in the morning prior to dialysis than after and more likely to occur in patients receiving a total daily insulin dose greater than 0.23 units/kg/day [32]. Additionally, the complex logistics of inpatient hemodialysis can result in missed meals and inconsistent dosing of scheduled medications including insulin which can contribute to glycemic variability.

Hyperkalemia Treatment

Hyperkalemia is frequently encountered in hospitalized patients with advanced kidney disease and usually treated with 10 units of intravenous regular insulin and 25 g of dextrose. Unfortunately, 6–22% of patients experience hypoglycemia with this therapy [33–35]. Alternate strategies utilizing a lower fixed dose of regular insulin of 5 units or a weight-based dose of 0.1 unit per kilogram (maximum 10 units) have been shown to reduce hypoglycemia risk without significantly affecting potassium reduction [36]. In the authors experience, alternate dose therapy can still cause hypoglycemia when pretreatment glucose is below 150 mg/dl and using higher doses of dextrose (50 g) in these patients can help prevent that [37]. Close glucose monitoring posttreatment for all patients undergoing hyperkalemia treatment is suggested.

Peritoneal Dialysis (PD)

Some patients prefer peritoneal dialysis as it offers convenience of completing this procedure at home. The high dextrose concentrations of peritoneal dialysate (1.5–4.5%) absorbed from the peritoneal membrane can cause significant hyperglycemia. The dextrose concentration of the dialysate solution and timing of PD cycles should guide subcutaneous insulin management. A reasonable subcutaneous insulin strategy is to give NPH or detemir at the start of evening PD or regular insulin at the start of PD and 6 h post-PD initiation. An initial insulin dose of 10% of TDD for 2.5% dextrose concentrations or 20% of TDD for 4.5% dextrose solution can be given with careful dose titration and close glucose management as PD patients can be insulin-sensitive and predisposed to hypoglycemia [38].

Intraperitoneal insulin given with the dialysate solution can be convenient and, in some studies, can achieve better glycemic control with less hypoglycemia and reduce formation of insulin antibodies. It is important to note that insulin requirements can increase by up to 30% when switching from a subcutaneous regimen due to insulin adherence to the plastic bag and tubing [39, 40]. Complications from intraperitoneal administration of insulin include peritonitis and subcapsular steatosis.

Non-insulin Antidiabetic Agents

Current standard of care recommendations from the American Diabetes Association and Endocrine Society advise discontinuing oral and non-insulin-injectable medications upon admission for most patients with diabetes [21, 41]. Utilizing non-insulin agents in the hospital is an area of intense study. Hospitalization presents many

challenges to the safe use of oral agents such as alteration and interruption of normal dietary habits, infection, surgical procedures, administration of IV contrast dye, and acute changes in renal function. Nevertheless, these agents may be appropriate to initiate or continue in select patients who are otherwise stable and eating regularly and have no contraindications. Salient features for inpatient use of oral agents are described below, and their dose adjustments for renal dysfunction are outlined in Table 23.1.

Dipeptidyl Peptidase 4 Inhibitors

Dipeptidyl peptidase 4 inhibitors (DPP4i) reduce the breakdown of incretin hormones leading to insulin secretion in a glucose-dependent manner and have been shown to be safe and effective in patients with renal impairment and ESRD. They are effective as monotherapy in CKD and mild inpatient hyperglycemia as suggested by a recent update by Endocrine Society which also describes their role in combination with either correction insulin or long-acting insulin therapy in patients with “moderately well-managed” T2DM (HbA1c <7.5%, BG <180 mg/dL, total daily insulin <0.6 units/kg/day) hospitalized for a noncritical illness [42]. These drugs reduce insulin requirements, frequency of nursing intervention for prandial insulin, and the frequency of hypoglycemic events when used alone or in combination with basal insulin [25] compared to standard basal-bolus insulin regimens [43–46]. With the exception of linagliptin, dose adjustment is needed in CKD Stage 3 and higher. Saxagliptin, although evaluated in the hospital setting [47], should be avoided in patients with or at risk for HF along with alogliptin [55, 56].

Glucagon-Like Peptide-1 Receptor Agonists

While glucagon-like peptide-1 receptor agonists (GLP-1RAs) are recommended in patients with or at risk of diabetic kidney disease in the outpatient setting (especially those with higher BMIs), they are started with caution in the acute care setting as they frequently cause nausea and vomiting which can precipitate acute on chronic renal dysfunction. Outpatient studies evaluating liraglutide and dulaglutide have shown they are safe in moderate to severe renal dysfunction [48, 49]. Inpatient use has shown they can help improve glycemic control, reduce overall insulin requirements, and potentially reduce hypoglycemic episodes, but short-acting formulations can have up to a sixfold increase in nausea and/or vomiting [42, 50, 51]. While they do not cause hypoglycemia when used alone, they increase the risk of hypoglycemia with concomitant use of insulin or insulin-secretagogues. Several studies have also evaluated intravenous GLP-1RAs in the intensive care unit compared to insulin drips. In one study, patients receiving intravenous liraglutide had fewer episodes of hypoglycemia and less glycemic variability than those on insulin drip alone [52].

Table 23.1 Renal dose adjustments of non-insulin antihyperglycemic medications

| Class | Drug name | Renal adjustments eGFR <60 mL/min | Dialysis adjustments | Comments |
|--------------------|---------------------------------------|--|--|--|
| Biguanides | Metformin | eGFR <45 mL/min: 500 mg BID max dose Do not initiate but can continue eGFR <30 mL/min: contraindicated | Contraindicated | Contraindicated in ESRD due to risk of lactic acidosis |
| Sulfonylureas | Glimepiride Glipizide Glyburide | Glipizide: eGFR <50 mL/min—2.5 mg daily Glimepiride: eGFR 15–60 mL/min—1 mg daily, titrate cautiously eGFR <15 mL/min—avoid use Glyburide: avoid in CKD | Glipizide 2.5 mg daily with slow titration as needed (use with caution) | Glyburide contraindicated in ESRD due to risk of severe hypoglycemia |
| Glinides | Nateglinide Repaglinide | Nateglinide: eGFR <30 mL/min—60 mg with meals eGFR <15 mL/min—avoid d/t accumulation of active metabolite Repaglinide: eGFR <40 mL/min—0.5 mg with meals | Repaglinide 0.5 mg with meals (has not been extensively studied in hemodialysis patients) Nateglinide should be used with caution in hemodialysis patients due to active metabolite | Similar hypoglycemia risk as sulfonylureas. Should only be used in patients who are eating |
| Thiazolidinediones | Pioglitazone | None | None | Avoid in CHF due to edema/fluid retention Avoid in patients with hepatic insufficiency |

(continued)

Table 23.1 (continued)

| Class | Drug name | Renal adjustments eGFR <60 mL/min | Dialysis adjustments | Comments |
|----------------------------|--|---|--|--|
| SGLT-2 inhibitors | Canagliflozin Dapagliflozin Empagliflozin Ertugliflozin | Canagliflozin: eGFR <60 mL/ min—100 mg daily eGFR <25 to 30 mL/min—do not initiate but can continue 100 mg daily Dapagliflozin: eGFR ≥25 mL/ min—10 mg daily eGFR <25 mL/ min—do not initiate but can continue 10 mg daily Empagliflozin: eGFR <30 to ≥20 mL/ min—10 mg daily eGFR <20 mL/ min—do not initiate but can continue 10 mg Ertugliflozin: eGFR <45 mL/ min—not recommended Note: evidence of the safety and efficacy of SGLT2i in CKD is still emerging, and it is likely the lower threshold for use of these agents will likely decrease in the future | Contraindicated | SGLT2-i's have shown benefit in preserving renal function and heart failure in patients with lower eGFRs SGLT2-i's should be held 3–4 days prior to scheduled procedures and in patients with poor dietary intake/NPO status due to risk of euglycemic DKA |
| GLP-1 receptor agonists | Dulaglutide Exenatide Liraglutide Semaglutide | Dulaglutide, Liraglutide, Semaglutide: no dose adjustment necessary Exenatide: eGFR <30 mL/ min: not recommended | Dulaglutide, Liraglutide, Semaglutide: Use with caution, limited clinical evidence Exenatide: not recommended | Should be used with caution due to nausea, vomiting, and diarrhea as well as increased risk of AKI |

Table 23.1 (continued)

| Class | Drug name | Renal adjustments eGFR <60 mL/min | Dialysis adjustments | Comments |
|------------------|---|--|---|---|
| DPP-4 inhibitors | Alogliptin Linagliptin Sitagliptin Saxagliptin | Alogliptin: eGFR ≥30 to <60 mL/min— 12.5 mg daily eGFR <30 mL/ min—6.25 mg daily Linagliptin: no dose adjustment Saxagliptin: eGFR <45 mL/ min—2.5 mg daily Sitagliptin: eGFR ≥30 to <45 mL/min— 50 mg daily eGFR <30 mL/ min—25 mg daily | Alogliptin: 2.5 mg daily Linagliptin 5 mg daily Saxagliptin: 2.5 mg daily Sitagliptin: 25 mg daily | Linagliptin 5 mg daily is preferred in CKD patients as no renal dose adjustment is necessary Reduce daily dose for all drugs except linagliptin Saxagliptin and Alogliptin are not recommended in heart failure patients |

The GI side effects, cost, need for prior authorization, and their availability for subcutaneous use as pen devices currently limits their initiation in the hospital setting. Potential use is limited to stable patients using GLP-1RAs prior to admission, if patients' own medication are allowed in the facility. GLP-1RAs should be avoided in patients with a history of pancreatitis or at risk for medullary thyroid cancer.

Biguanides

Guidelines currently recommend metformin as the first-line agent for most patients with T2DM and CKD with an eGFR ≥ 30 mL/min [18, 53]; however in the inpatient setting, they are initiated only for stable patients and those close to discharge as the rare but serious adverse effect of lactic acidosis occurs concurrently with acute illness, especially acute kidney injury. Renal function should be assessed prior to starting or continuing metformin and should be monitored periodically throughout hospitalization. Metformin may be continued in patients with an eGFR between 30 and 45 mL/min at a maximum dose of 500 mg BID, but is contraindicated in patients with an eGFR <30 mL/min and those on dialysis. The FDA currently recommends that metformin should be held on the day of scheduled surgery and for 48 h following use of iodinated contrast in patients with an eGFR of <60 mL/min or those with a history of liver disease, alcoholism, or heart failure. According to a recent joint consensus statement from the American College of Radiology and the National Kidney Foundation, the risk of contrast-associated acute kidney (CA-AKI) injury in patients taking metformin with an eGFR 30–59 mL/min is minimal and should

generally only be held if the patient is at high risk of CA-AKI [54]. At this time, practice may vary as hospital policy and protocol may differ between institutions.

Sulfonylureas

Sulfonylureas are insulin secretagogues cleared mainly by the kidney; therefore, longer-acting sulfonylureas such as glyburide and glimepiride cause prolonged hypoglycemia. While glipizide is the preferred sulfonylurea in patients with CKD and ESRD, the benefits of continuing should be weighed against the risk of hypoglycemia. In some patients, hospitalization can be an opportunity to consider alternative antihyperglycemic options post-discharge.

Glinides

Repaglinide and nateglinide are also insulin secretagogues and carry a lower risk of hypoglycemia than sulfonylureas due to their shorter duration of action as they are used for managing postprandial hyperglycemia. Nateglinide can be used in patients with an eGFR <30 mL/min starting at a lower dose of 60 mg with meals but should be avoided in patients with an eGFR <15 mL/min. Repaglinide can be used in patients with CKD/ESRD, but blood glucose should be monitored closely and should be started at the lowest dose of 0.5 mg before meals with slow titration.

Thiazolidinediones

Thiazolidinediones are cleared by the liver; however their potential risk of fluid retention, especially with use of insulin, reduces their benefit in the inpatient setting, particularly in patients with or at risk of heart failure. As they target the PPAR gamma nuclear receptor, their glycemic benefit is delayed. Additionally, they increase the risk of fractures in women which is particularly concerning in ESRD patients already prone to mineral metabolism abnormalities [55].

Sodium-Glucose Transport Protein 2 Inhibitors

Sodium-glucose cotransporter protein 2 inhibitors (SGLT2is) are less effective as glucose-lowering agents in patients with lower eGFRs <60 mg/dL [56, 57], but their use in the inpatient setting has increased dramatically in recent years due to evidence of significant reductions in cardiovascular outcomes and mortality,

particularly in the heart failure population. Data also supports the use of some of these agents in slowing the progression of renal disease [58–60]. A recent guideline update by the Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group recommends treating patients with T2DM, CKD, and an eGFR ≥ 20 mL/min with an SGLT2i and continuing to treat even if eGFR falls below 20 mL/min unless not tolerated or the patient requires hemodialysis or renal transplantation [61]. When initiating SGLT2is, it should be noted that a reversible decrease in eGFR has been demonstrated in clinical trials, but this modest initial decrease in eGFR is outweighed by the reduction in risk of cardiovascular disease progression [56]. SGLT2is are contraindicated in patients on dialysis and have not been well-studied in renal transplant patients who may benefit from these agents but may also be at an increased risk of infection due to immunosuppression. For inpatients with heart failure, recent studies including the EMPULSE, SOLOIST, and EMPA-RESPONSE trials emphasize the benefit of initiating these drugs during or immediately after hospitalization [5].

The US Food and Drug Administration recently revised labeling to recommend holding canagliflozin, dapagliflozin, and empagliflozin at least 3 days prior and ertugliflozin at least 4 days prior to scheduled surgical procedures due to the risk of euglycemic ketoacidosis [62]. Lastly, evidence on potential risk of lower-limb amputation with canagliflozin should be considered in patients with active foot infection in the setting of peripheral artery disease and polyneuropathy [63].

Management of DKA in Patients with ESRD

Up to 7.5% of patients in the United States admitted with diabetic ketoacidosis (DKA) have ESRD. The diagnosis and treatment of DKA is particularly challenging in this population due to alterations in baseline electrolyte and pH changes, glucose and insulin metabolism, limitations administering large volume fluid resuscitation, and impaired renal clearance of insulin and diabetes medication. In a recent publication which investigated the clinical characteristics and outcomes of patients with ESRD admitted with DKA concluded that when compared to a population with normal renal function, patients with ESRD were twofold more likely to have higher blood glucose on admission and rates of hypoglycemia, and tenfold more likely to have volume overload and mechanical ventilation. While they had similar mortality, patients with ESRD had longer lengths of stay and hospitalization costs when compared to patients with preserved renal function [7].

Significant fluid and electrolyte loss in DKA is via osmotic diuresis. Standard of care fluid resuscitation with isotonic saline at a rate of 15–20 mL/kg or 1–1.5 L during the first hour with subsequent rate of 250–500 mL/h in patients without cardiac or renal compromise may increase the risk of volume overload and pulmonary edema especially if this becomes more aggressive. The degree of hypertonicity and intracellular volume contraction is less profound in patients with ESRD [64]. A modified approach for fluid replacement such as administering an initial small bolus

of 250 mL with reassessment after each infusion may reduce the risk of pulmonary edema and subsequent intubation in this population. Since hypertonicity in this population is driven primarily by hyperglycemia rather than osmotic diuresis, it has been proposed that insulin administration alone, with limited fluid resuscitation, may correct the underlying metabolic derangements without significant complications [65]. Use of subcutaneous insulin DKA algorithms is a consideration in cases of mild to moderate DKA [66].

Current guidelines recommend titrating insulin infusion rates to lower glucose by 50–75 mg/dL/h. Potentially avoiding the intravenous insulin bolus when starting the insulin infusion can reduce the risk of hypoglycemia [12, 40].

A personalized and standardized approach to DKA management in renal dysfunction is necessary to improve outcomes and prevent iatrogenic complications such as volume overload and hypoglycemia, and more research is needed to develop specific DKA guidelines for this population.

Conclusion and Future Directions

Patients with renal disease have altered physiology of glucose and insulin metabolism making them a vulnerable group of hospitalized patients who have significant glucose variability especially in advancing kidney dysfunction and around dialysis. They are especially prone to hypoglycemia which can be exacerbated by unadjusted glucose goals and antihyperglycemic treatments. Identifying glucose patterns using CGMs to alter BG goals and treatment strategies can help keep these patients safe in the hospital. Management of DM patients with CKD is an area of active research especially for treatment targets and use of wearable technology.

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Chapter 24

Diabetes Care in the Oncologic Population



Lubaina S. Presswala, Azeez Farooki, and James Flory

Introduction

Diabetes has been associated with an increased risk for a variety of cancers, particularly pancreatic, colorectal, breast, liver, endometrial, and bladder cancer [1]. Diabetes and cancer commonly co-exist and outcomes in patients with both conditions are poorer than in patients with cancer who do not have diabetes [2]. There are no randomized controlled trial data indicating that hyperglycemia treatment improves cancer-related outcomes such as progression-free or overall survival, so a practical approach to hyperglycemia should be implemented that prioritizes prevention of the known short-term complications of hyperglycemia (e.g., electrolyte disturbances, volume depletion, catabolic weight loss, and possibly infection). A secondary but still important advantage of glycemic control for patients who are likely to enter long-term survivorship is prevention of longer-term microvascular and macrovascular complications of diabetes [3–5].

In this chapter, we will briefly review the relationship between diabetes and cancer and then focus on diabetes management in patients with cancer. We use

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the terms “diabetes” and “hyperglycemia” interchangeably throughout this chapter, acknowledging that it may be unclear whether some transient forms of hyperglycemia (e.g., due to steroid use) should be classified as diabetes. Glucocorticoid-induced hyperglycemia and worsening of diabetes are particularly common challenges in the management of patients with cancer and a major focus of this chapter. Additional areas of focus in this chapter include management of chemotherapy-mediated hyperglycemia, immunotherapy-mediated type 1 diabetes mellitus (T1DM), paraneoplastic hyperglycemia, diabetes management during end-of-life care, and diabetes management in patients with challenging nutritional status (e.g., malnutrition, anorexia, cachexia, and enteral or parenteral nutrition).

Diabetes and Cancer Incidence

The underlying mechanisms involved in the development and progression of cancer are multifactorial. Chronic inflammation, hyperinsulinemia, changes in the levels of adipokines, inflammatory cytokines, growth hormones, gut microbiome, and free fatty acids are few known culprits involved with metabolic alterations associated with tumor development and progression [6, 7]. Obesity-induced insulin resistance and metabolic syndrome as seen in type 2 diabetes mellitus (T2DM) play a pathogenic role in contributing to increased cancer incidence and cancer-specific mortality [6, 8]. It is important to note that waist circumference is preferred over body mass index (BMI) as it relates to visceral “inflamed” adiposity, which may be a resourceful habitat to a cancer cell [8]. This also supports the increased risk of certain cancers in people with metabolic dysfunction, albeit with normal BMI [7].

A meta-analysis performed in 2007 with 221 datasets from different populations found that in men, for every 5 kg/m² increase in BMI, there was an increased risk of esophageal (RR 1.52, $p < 0.0001$), thyroid (1.33, $p = 0.02$), colon (1.24, $p < 0.0001$), and renal (1.24, $p < 0.0001$) cancers [9]. In women, an increased risk of endometrial (1.59, $p < 0.0001$), gallbladder (1.59, $p = 0.04$), esophageal (1.51, $p < 0.0001$), and renal (1.34, $p < 0.0001$) cancers was noted [9]. Overall, a consistent increase in the risk of pancreatic cancer, biliary tract cancer, and esophageal cancer in men; breast and endometrial cancer in women; and kidney and colorectal cancer in men and women has been reported in patients with obesity and insulin resistance related T2DM [10–16]. In contrast to T2DM, type 1 diabetes has not been linked with the same pattern of increased risk of cancer, possibly due to the lack of insulin resistance and metabolic dysfunction in these patients. A small number of studies that have examined this association were mainly with Swedish cohorts with notably increased risks of stomach, cervical, endometrial, squamous cell cancer, and leukemia [17, 18] in patients with T1DM.

Diabetes and Cancer Outcomes

Studies on cancer-specific mortality have revealed that patients with diabetes have greater cancer mortality compared with patients without diabetes [19, 20]. It is far less clear whether improved control of diabetes would improve mortality or other cancer-related outcomes. Observational data are generally inconclusive on this question. For example, Cheung and colleagues compared cancer progression and mortality in metastatic breast cancer (MBC) between 244 patients with diabetes and 244 without diabetes [21]. Diabetes was not associated with increased mortality at 5 years, and assessment of good glycemic control (glucose <180 mg/dL) versus poor glycemic control (glucose >180 mg/dL on 2 occasions in 1 month) also did not show that worse glycemic control was associated with increased mortality in individuals with MBC at 5 years or with more rapid progression to a second line treatment for cancer. However, this study had methodological limitations including small size and limited ability to adjust for potential confounders of outcomes. Another study by Lin and colleagues investigated whether glycemic control impacted mortality in patients with prostate cancer and existing diabetes, in a cohort of 831 patients including 141 with diabetes mellitus and data on glycosylated hemoglobin A1c (HbA1c) [22]. Patients with HbA1c >9% ($n = 14$), but not those with HbA1c $\leq 9\%$, had significantly increased risk for all-cause and non-prostate cancer mortality but not for prostate cancer-specific mortality [22]. These cohort studies represent a consistent pattern in the literature that poor glycemic control is frequently associated with worse clinical outcomes, but there is little evidence that the association is cancer-specific and high potential that the association is due to confounding by comorbidities and other risk factors that are more common in patients with diabetes and hyperglycemia. Without randomized data, it would be premature to conclude that tighter glycemic control will (or will not) improve cancer-related outcomes. Nonetheless, as explained in the remainder of the chapter, glycemic control remains an important aspect of supportive care.

Diabetes Management in the Oncologic Population

Glycemic Targets

Glycemic targets for patients with cancer should generally be less stringent than those used for the broader population of patients with diabetes. HbA1c <7% is a typical goal for glycemic control for patients with diabetes, with inpatient noncritical care glycemic targets ranging from 140 to 180 mg/dL. In contrast, the American Diabetes Association (ADA) and American Association of Clinical Endocrinologists (AACE) guidance suggest less stringent hemoglobin A1C goals (such as <8% [64 mmol/mol]) may be appropriate for patients with limited life

expectancy or where the harms of treatment are greater than the benefits [23, 24]. This is pertinent to the oncologic population based on the severity of their cancer [24].

There may be no empiric need to loosen glycemic targets for patients with diabetes and without active cancer or on active cancer treatment, provided they are doing well on their existing anti-diabetes regimen. However, the provider needs to work with the individual patient and should consider adjusting targets or simplifying the regimen if this change is needed to improve safety and adherence [23]. Given the scarcity of data showing benefits from glycemic control on overall survival or disease-specific survival for patients with cancer, it is reasonable to aim for less stringent glycemic targets tailored to the patient in the inpatient and outpatient settings. For example, in a patient with very limited life expectancy, the appropriate goal is to avoid hyperglycemia so severe that the patient develops acute symptoms such as polyuria. This could amount to a goal of <250 mg/dL serum glucose or even higher, depending on the patient.

Glucocorticoid (Steroid)-Induced Hyperglycemia

Glucocorticoids (GC), also known as steroids, are a mainstay of many chemotherapy regimens in patients with cancer. They are used for their immunosuppressive, immunomodulatory, and anti-emetic properties. GCs have many additional side effects including a profound effect on carbohydrate metabolism that in broad terms appears to relate to transactivation of multiple genes and does not have a single mechanism [25]. GCs target different processes of the insulin signaling cascade and protein interactions and alter substrate binding properties that can potentially mediate ineffective insulin release and action reducing insulin-stimulated glucose uptake at terminal sites [26]. The hyperglycemia seen with GC involves impaired insulin signaling activity, reduced insulin-stimulated glucose uptake, and increased gluconeogenesis. While GC can lead to both insulin deficiency and insulin resistance, clinically one of the more striking effects is the insulin resistance, which occurs at the level of the skeletal muscle, liver, and adipose tissue.

The incidence of GC-induced hyperglycemia varies in the range of 12–70% in the general population without pre-existing diabetes mellitus [26–29]. The prevalence of steroid-induced hyperglycemia (SIH) was 39% in patients hospitalized with hematologic malignancies [30]. There has been evidence on hazard ratios of approximately 1.30 or greater in multiple studies for incident diabetes mellitus in patients on glucocorticoids [26, 31, 32]. There are no standard diagnostic criteria for GC-induced hyperglycemia, which depending on the study has been defined based on fasting glucose levels of ≥ 126 mg/dL or ≥ 140 mg/dL, or random glucose levels of ≥ 180 mg/dL or ≥ 200 mg/dL. While GC-induced hyperglycemia often resolves after discontinuation of glucocorticoids, GC-associated diabetes mellitus is characterized by persistent hyperglycemia after discontinuation of GC that satisfies

diagnostic criteria for T2DM based on fasting or random blood glucose thresholds [33]. Chapter 12 in this textbook elaborates specifically on GC associated hyperglycemia in the general hospital population.

The clinical implications of GC-induced hyperglycemia have not been clearly established. However, hyperglycemia was a predictor of hospital length of stay among patients without diabetes (but not patients with diabetes) and with acute leukemia or stem cell transplant [30]. The pattern of glycemic excursions observed is associated with the type of steroid, its dose, and duration. While replacement steroid doses roughly equivalent to physiological levels of endogenous cortisol may only minimally raise glucose levels, hyperglycemia can be profound in those on moderate to high doses of corticosteroids, such as 7.5–30 mg and 30 mg per day of prednisone and prednisolone, respectively [34, 35]. When intermediate acting GCs are administered once daily (in the morning), hyperglycemia is more marked 4–8 h [36] after the dose (seen mostly in late afternoon and evening time). However, when GCs are administered in two to three divided doses or in the case of long-acting GCs such as dexamethasone, hyperglycemia may be continuous throughout the day with a substantial impact on fasting values [34, 35]. Short acting GCs cause a greater degree of post prandial hyperglycemia due to insulin resistance. Therefore, a normal fasting blood glucose may be misleading, while most hyperglycemia persists throughout the day.

Both patient-related and steroid-related factors are relevant at the outset of inpatient glycemic management for patients with cancer on glucocorticoids. Patient related factors include any pre-existing history of diabetes, prediabetes, or steroid induced hyperglycemia. With a known history of diabetes, relevant history includes the duration of diabetes, glycemic control at home (based on HbA1c or average self-monitored blood glucose (SMBG) readings), microvascular or macrovascular complications, and home diabetes management regimen. Steroid-related factors include the type of steroid used, time action profile of steroid, the frequency of steroid administration, and the short-term or long-term dose schedule for the patient. Particularly, when steroids are used to abrogate the side effects of chemotherapy, it is common for steroids to be given for a few days at a time, with days or weeks without steroids between each cycle of treatment. In that scenario, more aggressive “steroid day” versus “non steroid day” insulin dosing regimens are helpful. Table 24.1 illustrates the commonly used steroids in the hospital setting and their pharmacokinetic properties [36–38].

Table 24.1 Pharmacokinetics of commonly used glucocorticoids [36–38]

| | Hydrocortisone | Prednisone | Methylprednisolone | Dexamethasone |
|-----------------------|----------------|------------|--------------------|---------------|
| Hyperglycemic effects | | | | |
| Onset | 1 h | 4 h | 4 h | 4 h |
| Peak | 4–6 h | 8 h | 8 h | Unknown |
| Resolution | 8–12 h | 12–16 h | 12–16 h | 24–36 h |
| Elimination half-life | 2 h | 2–4.5 h | 2–4.5 h | 3–5 h |
| Biologic half-life | 5–24 h | 12–36 h | 12–36 h | 36–72 h |

The patient's baseline renal and hepatic function, nutritional status, and history of gastrointestinal disease should be factored in assessing the optimal agent for the management of GC-induced hyperglycemia. Most oral and non-insulin injectable agents are not ideal in the hospital setting due to their slow onset of action and adverse effect profile such as gastrointestinal distress (as in the case for glucagon-like peptide 1 agonist and biguanides), hypoglycemia (sulfonylureas and meglitinides), and fluid retention (thiazolidinediones). The use of these agents is also limited since many hospitalized patients with cancer are also dehydrated and malnourished due to their underlying malignancy or adverse effects from chemotherapy. Sodium-glucose cotransporter 2 inhibitors (SGLT2i) may not be appropriate in anorexia or dehydration, and evidence is scarce on the use of these agents for GC-induced hyperglycemia in hospitalized patients with cancer.

Management of GC-induced hyperglycemia in the inpatient setting typically involves the use of either neutral protamine Hagedorn (NPH) insulin or a combination of basal-bolus insulin with an additional rapid acting correctional insulin scale based on the patient's body weight or previously known insulin regimen used at home. The RABBIT 2 trial reported that basal-bolus regimens resulted in greater improvement in glucose control than correctional insulin alone in patients with T2DM [39]. Table 24.2 illustrates the pharmacokinetics of the commonly used insulins in the hospital setting [40–45].

In the case of basal-bolus insulin, patients typically require more bolus insulin versus basal insulin to specifically address the post-prandial hyperglycemia due to steroid-related insulin resistance [36]. The known pharmacokinetics of steroids and insulin allow for safe and effective management of hyperglycemia in the inpatient setting. Figure 24.1 illustrates the most used glucocorticoid and insulin time action profile, superimposed data from Tables 24.1 and 24.2 [36–38, 40–45]. As noted in the figure, hydrocortisone's relative effects follow a similar time action profile as intermediate acting insulin (NPH). Prednisone or prednisolone effects may also be mitigated by intermediate acting insulin (NPH) with or without the need for pre-meal rapid-acting or short-acting insulin. The prolonged effects of

Table 24.2 Pharmacokinetics of commonly used insulins [40–45]

| | Onset | Peak | Duration |
|--|-----------|-------------------|-----------|
| Ultra long-acting insulin (degludec) | 0.5–2 h | 12 h (minimal) | 40+ h |
| Ultra long-acting insulin (glargine U300) | 4–6 h | 12–16 h (minimal) | 18–25+ h |
| Long-acting insulin (detemir, glargine) | 1–2 h | None/minimal | 18–24 h |
| Intermediate-acting insulin (neutral protamine hegadorn—NPH) | 1–2 h | 2–8 h | 12–16 h |
| Short-acting insulin (human regular insulin) | 30–60 min | 2–4 h | 5–8 h |
| Rapid-acting insulin (lispro, aspart, glulisine) | 10–30 min | 0.5–3 h | 3–5 h |
| Ultra-rapid acting insulin (faster insulin aspart) | 4–15 min | 0.5–2.2 h | 5–7 h |
| Ultra-rapid acting insulin (faster insulin lispro) | 2–20 min | 1 h | 4.6–7.3 h |

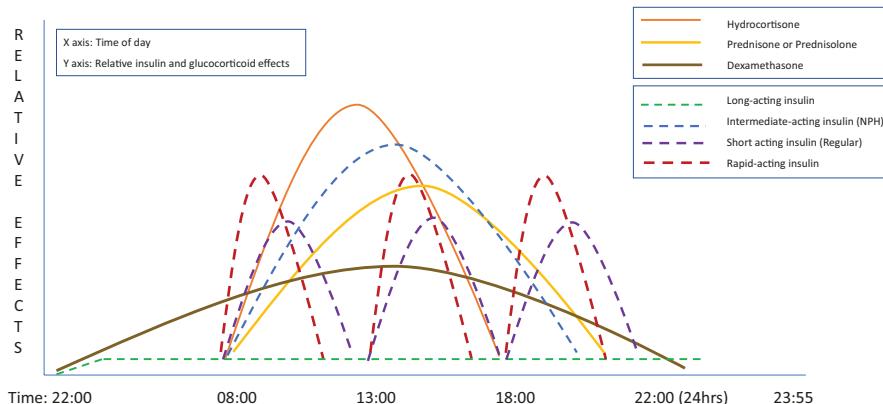


Fig. 24.1 Most used glucocorticoids and insulin time action profile [36–38, 40–45]

dexamethasone may be optimally mitigated by basal and bolus insulin coverage [36–38, 40]. Figure 24.2 illustrates an example algorithm for inpatient management of glucocorticoid-induced hyperglycemia or diabetes developed at the authors' institution, as a guide for insulin initiation and intensification that can be applied to the hospitalized patient with or without any cancer [34]. Once the patient is approaching discharge, other oral or non-insulin injectable agents can be considered with or without insulin based on the degree of hyperglycemia, steroid frequency, and other factors such as accessibility and patient adherence to these agents.

Biguanides such as metformin may be added to this management strategy if there are no contraindications. Short report of observational studies published in 2005 suggested that the use of metformin was associated with a 23% decreased risk of any cancer [46]. A careful assessment of the observational studies conducted from 2006 to 2012 point to some important time-related biases that systematically exaggerated the reported antitumor effects of metformin [47]. Some meta-analysis published from 2013 to 2018 is suggestive of Metformin's protective effects; however, limitations in their methods, inability to exclude confounding variables (such as additional use of statins), and failure to account for time related biases should urge clinicians to interpret this data very cautiously [48–50]. In a randomized controlled trial by Goodwin et al., 3649 patients with high-risk operable breast cancer without diabetes were randomized to metformin 850 mg twice a day or placebo twice a day for 5 years [51]. Treatment with metformin versus placebo resulted in a hazard ratio for an invasive disease-free survival event of 1.01; which was not statistically significant [51]. This study was conclusive that the addition of metformin to standard breast cancer treatment did not significantly improve invasive disease-free survival [51]. Considering these results and previous observational studies, it is reasonable to validate metformin as a robust insulin sensitizer in the case of insulin resistance; however, its effect on cancer is still not well understood.

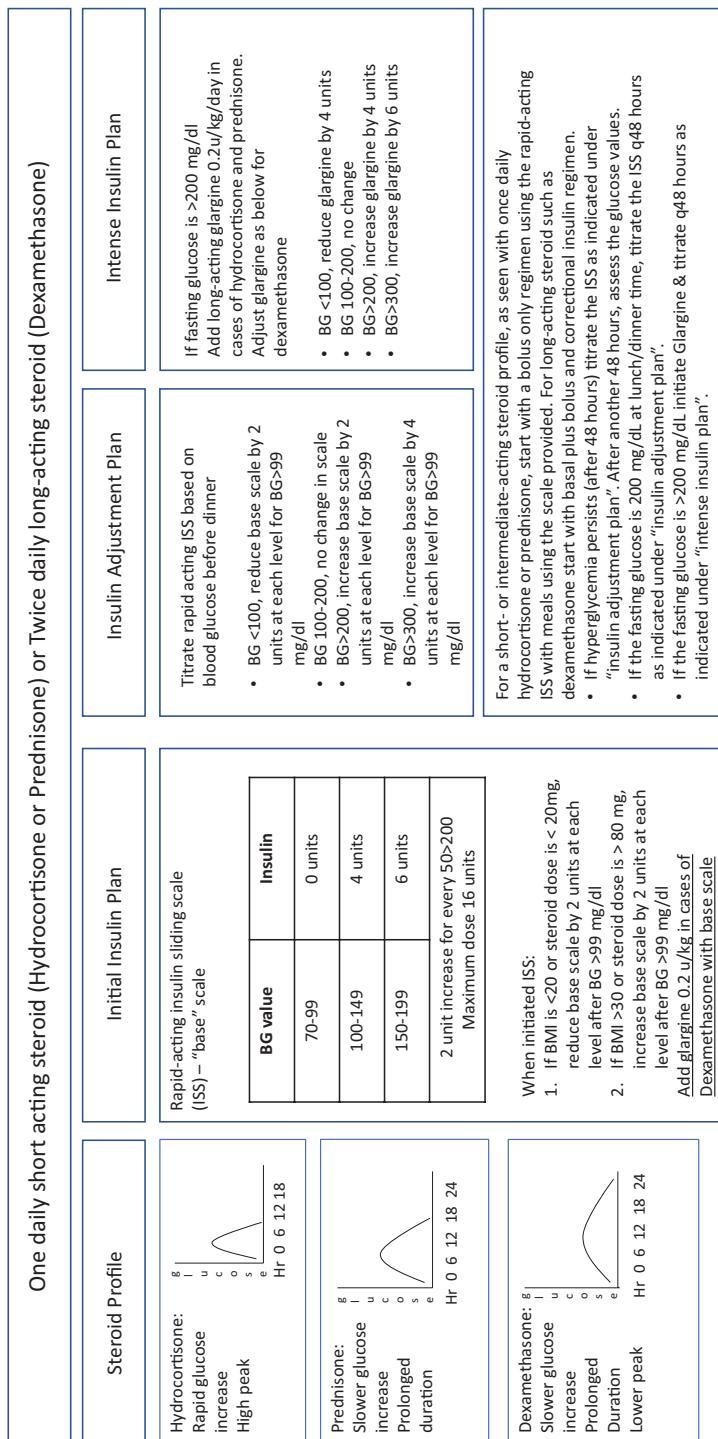


Fig. 24.2 New onset glucocorticoid induced hyperglycemia example algorithm for patients with or without cancers [34]

Chemotherapy-Mediated Hyperglycemia

A systematic review of 22 studies [52] supported the hypothesis that certain chemotherapeutic agents are associated with an increased risk of hyperglycemia in patients with solid tumor cancers. Androgen deprivation therapy, docetaxel, temsirolimus, and interferon-alpha increased the risk of hyperglycemia when used alone or in-combination with other agents [52]. Tacrolimus is also known to be a potent inhibitor of insulin secretion [53]. Weaker evidence suggest 5-fluorouracil, paclitaxel, cisplatin, and gemcitabine could potentially increase the risk of hyperglycemia in patients with cancer [52].

The mechanistic target of rapamycin (mTOR) inhibitor everolimus is an antitumor agent that has been particularly well established as causing hyperglycemia [54]. Hyperglycemia is reversible in patients once everolimus is discontinued [54]. The theoretical basis is postulated to be impaired insulin secretion leading to increased basal hepatic glucose production [54]. Hyperglycemia may present approximately 3–8 weeks after everolimus administration and insulin, insulin sensitizers, or secretagogues usually help mitigate hyperglycemia [30]. The highest incidence of everolimus-mediated hyperglycemia was reported in patients with renal cell carcinoma (27.2%) and the lowest incidence in patients with breast cancer (3.3%) in a meta-analysis ($n = 3879$ cancer patients) of seven phase III and two phase II randomized controlled trials [55].

Phosphatidylinositol 3-kinase (PI3K) inhibitors are an emerging class of antitumor therapy with a strong link to hyperglycemia. PI3Ks are a family of enzymes that mediate the intracellular effects of insulin. PI3K α is a heterodimer made of a regulatory subunit (p85 α) and a catalytic subunit (p110 α), the latter of which is encoded by the gene PIK3CA and is ubiquitously expressed in all cell types. PI3K enhancement is a hallmark of cancer in humans, and PIK3CA is the most frequently mutated oncogene in breast cancer [56]. Blockade of PI3K α creates a transient state of insulin resistance and hyperglycemia, a common adverse event observed in all large clinical trials of PI3K α inhibitors [57, 58].

Alpelisib, which is indicated for metastatic breast cancer with activating PIK3CA mutations, is among the best studied of these agents. SOLAR-1 trial assessed the safety and efficacy of alpelisib in combination with fulvestrant for patients with metastatic breast cancer [57]. In the PIK3CA-mutated cohort, longer median progression-free survival was observed in patients treated with alpelisib plus fulvestrant ($n = 169$) compared with placebo plus fulvestrant ($n = 172$) (11 months vs. 5.7 months; hazard ratio [HR] 0.65, $P < 0.001$) [57]. Hyperglycemia (fasting plasma glucose (FPG) >125 mg/dL) was among the most noted adverse events, reportedly 65% of the alpelisib-treated patients; out of which 37% met criteria for grade 3 (FPG > 250 – 500 mg/dL or random blood glucose (RBG) >300 mg/dL) or higher for hyperglycemia [57]. With alpelisib use, median time to onset of grade 2 (FPG > 160 – 250 mg/dL or RBG >200 mg/dL) worse hyperglycemia was 15 days [57]. The study protocol was later amended to only include patients with HbA1c $<6.5\%$ or FPG <140 mg/dL to avoid discontinuation of alpelisib for effects on

primary breast cancer outcomes [57]. Incidence of severe hyperglycemia (40.3% vs 32.9%) and discontinuation due to hyperglycemia (any grade: 9% vs. 3.6%; grade 3/4: 5.6% vs. 2.9%) were lower in the second half compared with the first half of patients randomized to alpelisib in SOLAR-1 [57]. Thus, implying that hyperglycemia is mitigated after drug discontinuation in most patients. Currently, there are no clear guidelines on how to manage hyperglycemia during alpelisib therapy if metformin fails. A review of the literature revealed a case series [56] implementing very low carbohydrate diets and utilizing SGLT2-inhibitors for the management of alpelisib-mediated hyperglycemia. However, caution is advised given the risk of euglycemic diabetic ketoacidosis (DKA) with SGLT2i in the setting of PI3K inhibitors [59–61]. Management of hyperglycemia may necessitate interruption of PI3K inhibitor treatment or cessation. Use of insulin therapy in order to continue a PI3K inhibitor is controversial since insulin could in theory stimulate the PI3K pathway; however, there is no human data confirming that this effect is clinically relevant [62].

Immunotherapy Mediated New Onset Type 1 Diabetes Mellitus

Immunotherapy with drugs that block immune checkpoints have emerged as an important intervention for an increasingly wide array of cancer indications. Immune checkpoints include cytotoxic T-lymphocyte antigen 4 (CTLA-4) and its receptors CD80/86, along with programmed cell death protein 1 (PD-1) and its ligand (PD-L1) [63]. Immune checkpoint blockade inhibits negative immune regulation, allowing an immune response directed toward cancer cells. Monoclonal antibodies directed against CTLA-4, PD-1, and PD-L1 are used in the treatment of many advanced cancers, including melanoma, lung cancer, renal cancer, head and neck cancers, urothelial cancers, and others [64]. The clinically approved CTLA-4 inhibitor is ipilimumab, while current PD-1 inhibitors are nivolumab and pembrolizumab, and PD-L1 inhibitors include atezolizumab, avelumab, and durvalumab. Inhibition of immune checkpoints can also cause immune-related side effects, especially autoimmunity directed toward self-tissues [63, 64]. One such side effect is type 1 diabetes mellitus (T1DM), also known as checkpoint inhibitor associated diabetes mellitus (CIADM) or immune checkpoint inhibitor (ICI) mediated diabetes mellitus (ICI-DM). This entity is rare but can present with life-threatening diabetic ketoacidosis and is predominantly linked to anti-PD-1/PD-L1 therapies [63, 64]. The median duration until diabetes onset after the start of anti-PD1/PD-L1 treatment was 49 days [63] as per a systematic review and meta-analysis. Antibodies directed toward glutamic acid decarboxylase (GAD65) have been the most reported among patients [63, 65]. Patients are more likely to present within a shorter timeframe and with diabetic ketoacidosis compared to those without antibodies at presentation. A retrospective chart review of 18 patients with ICI-DM following anti-PD-1 and anti-PD-L1 therapy highlighted the onset of diabetes at a median 2.5 months over 3 ICI cycles and 4.8 months over eight cycles, respectively [65]. The time to diagnosis was earlier among patients with positive

GAD65 autoantibodies. ICI-DM is abrupt and irreversible with notable pancreatic atrophy and can present with diabetic ketoacidosis among many patients at the time of diagnosis [65]. The approach to diabetes management in these patients consists of implementing basal-bolus insulin as normally used for the management of T1DM in patients without the history of ICI therapy. Patients with ICI-DM are especially likely to benefit from the use of a continuous glucose monitor (CGM) given the labile nature of T1DM.

Paraneoplastic Hyperglycemia

Paraneoplastic hyperglycemia is rare and challenging to manage. Ectopic adrenocorticotrophic hormone (ACTH) syndrome (EAS) is a frequent culprit for hyperglycemia related to paraneoplastic syndrome. Significant clinical vigilance is required in diagnosing ectopic ACTH mediated hyperglycemia; severe unexplained hypokalemia may be one laboratory clue. EAS is observed in 1–5% of small-cell lung cancer (SCLC) cases [66] and can be an endocrine emergency given its rapid and acute presentation. The diagnostic workup for EAS is complex and may require invasive testing (such as bilateral inferior petrosal sampling). Once carefully diagnosed by a comprehensive team of providers, patients are treated with tumor resection if possible and/or steroidogenesis inhibitors (such as ketoconazole, mifepristone, and metyrapone) for a goal reduction in their cortisol levels responsible for the hyperglycemia. Some patients may need additional anti-diabetes treatments (oral agents, non-insulin injectables or insulin) for palliation of hyperglycemia related symptoms. Case reports are also published on paraneoplastic hyperglycemia due to EAS in patients with bronchial carcinoids, metastatic prostate cancer, gastrointestinal stromal tumors, renal cell cancer, and metastatic Merkel cell carcinoma [67–70]. The suspicion of EAS should receive adequate attention and prompt evaluation to confirm the diagnosis and initiate rapid treatment to attain a more favorable prognosis.

Nutrition and Hyperglycemia

An assessment of the patient's nutritional status must be incorporated in the management of diabetes in patients with cancer. A prospective randomized trial of 50 inpatients in noncritical care units with diabetes on enteral nutrition therapy (ENT) suggested that majority of patients may require some form of basal insulin therapy for a reasonable degree of glycemic control in addition to sliding scale insulin versus sliding scale only [71]. Diabetes management is focused to their type of diabetes, baseline glucose control, GC treatment plan (see section "Glucocorticoid (Steroid)-Induced Hyperglycemia"), nutritional status or nutritional therapies (see Chaps. 27 and 28 on enteral and parenteral nutrition, respectively), and overall health.

Diabetes Management at the End of Life

Managing diabetes mellitus at the end-of-life revolves around the goal of de-prescribing with the intent of causing no harm. To date, there is little evidence comparing diabetes treatment strategies in patients with both diabetes and advanced disease, and several unanswered questions remain as how to best approach glucose management toward the end of life. A palliative medicine review [72] suggests using a disease-based framework that categorizes patients based on their level of advanced disease to set goals for diabetes management at the end of life. Patients with stable and active advanced disease with fair nutritional intake (such as metastatic cancers, dementia, cardiomyopathy) may have the prognosis of several months to a year, patients with impending death with organ or system failure with anorexia or cachexia (as seen in cases of fulminant liver failure, bone marrow failure) may have the prognosis of several days or weeks, and patients actively dying may have the prognosis of several hours to days. Diabetes management should be tailored to the patient based on the severity of their disease state with the goal to de-escalate their diabetes care and relax their blood glucose targets for palliative symptom control, while avoiding the risk of DKA and hyperosmolar hyperglycemic state (HHS). For patients with stable and active advanced disease, diabetes management may remain the same if the patient is instructed on how to monitor and manage extreme glycemic excursions of hypoglycemia and hyperglycemia [72]. In cases of renal failure, liver failure, anorexia, and progressive weight loss, oral diabetes agents and/or insulin may likely need dose reductions. Patients with type 1 diabetes should continue long-acting insulin for as long as possible to avoid DKA or with dose reductions to avoid any hypoglycemia [72]. For patients with impending death with organ or system failure with anorexia or cachexia, the goal of management is to avoid hypoglycemia due to anticipated dehydration, liver, and renal failure. Oral anti-diabetes agents may need significant dose reductions or may need to be stopped. Patients with T1DM would need significant reductions in their long-acting insulin dose with elimination of pre-meal and potentially correctional insulin [72]. SMBG checks are generally eliminated in patients with T2DM and used only where a decision needs to be made for management in patients with T1DM [72]. As in the previous two stages, a consensus on management is lacking for patients actively dying. Most practitioners in this case would simply withdraw all oral hypoglycemics and stop insulin in most cases of diabetes mellitus. At this point, care is focused on patient's comfort and preparatory bereavement counseling for caretakers and patients, where appropriate.

Conclusion

In conclusion, the medical literature offers little guidance, and is limited, on appropriately managing diabetes in the oncologic population. Understanding the pathophysiology of diabetes and having a thorough knowledge of the medications and

insulin regimen appropriate for use in patients with cancer should act as a framework for healthcare providers in formulating a safe and effective plan of care.

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Chapter 25

Inpatient Management of Children and Adolescents with Diabetes Mellitus



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Introduction

Diabetes mellitus (DM) is a syndrome of persistent hyperglycemia resulting from decreased insulin production or function [1]. Type 1 diabetes mellitus (T1DM) is caused by autoimmune-mediated destruction of the insulin-producing pancreatic β -cells [1]. Type 2 diabetes mellitus (T2DM) results from a combination of increased β -cell apoptosis and insulin resistance [1]. Although T1DM was previously referred to as juvenile-onset diabetes and type 2 diabetes as adult-onset diabetes, both type 1 and type 2 diabetes occur in the pediatric (and adult) population [1].

Children and adolescents with newly diagnosed DM require prompt medical attention and, in some cases, hospitalization for initial stabilization. Children and adolescents with established DM may also require hospitalization for diabetes-related complications, or for other reasons not directly related to diabetes. Regardless of the reason for hospitalization, diabetes is a dynamic condition requiring close clinical monitoring of glycemic control and adjustment of insulin administration. Here, we discuss the inpatient management of DM in children and adolescents hospitalized with new-onset type 1 or type 2 diabetes, diabetes-related complications, and other reasons resulting in dysglycemia.

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Hospital Admission Related to the Initial Diagnosis of Diabetes Mellitus

The American Diabetes Association (ADA) criteria [2] for the diagnosis of all types of diabetes in children and adolescents are a fasting plasma glucose level of ≥ 126 mg/dL (7 mmol/L), 2-h post prandial glucose level of ≥ 200 mg/dL (11 mmol/L), or a random plasma glucose level of ≥ 200 mg/dL (11 mmol/L) with associated symptoms such as polydipsia and polyuria. In addition, a hemoglobin A1c (HbA1c) level of $\geq 6.5\%$ is diagnostic as well, though in the absence of unequivocal hyperglycemia, the A1c result should be confirmed by repeat testing [2]. Following the diagnosis of T1D or T2D, if the patient is stable, initial management could be handled in the outpatient setting, which could involve a brief assessment in the Emergency Department (ED) especially if they are being sent from their primary care physician's office. However, if there is evidence for DKA, electrolyte abnormality, mental status changes, or if the patient is a young child, then the child or adolescent is sent to the ED for stabilization and further admission to the intensive care unit or the pediatric floor depending on the patient's status. This is crucial for the management of diabetes-associated dehydration and for ongoing evaluation for diabetes-related complications that would require an admission. Examples of these complications include diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar syndrome (HHS).

Diabetic Ketoacidosis (DKA)

DKA is a serious complication of DM marked by the following criteria: pH of <7.30 , blood glucose level of >200 mg/dL (11 mmol/L), serum bicarbonate of <15 mmol/L, elevated anion gap (>16 mmol/L), and evidence of ketonemia (serum β -hydroxybutyrate of ≥ 3 mmol/L) or moderate-large ketonuria [3]. The clinical features of DKA include polydipsia, polyuria, dehydration, tachycardia, tachypnea, Kussmaul respiration, acetone odor to breath, nausea and/or vomiting, abdominal pain, blurry vision, headaches, confusion, drowsiness, and progressive decrease in the level of consciousness [3]. The initial ED management for children with suspected DKA after routine assessment for airway, breathing, and circulation includes immediate establishment of intravenous (IV) access; measurement of blood glucose; serum electrolytes; blood gas; blood or urine ketones, in addition to the assessment of severity of dehydration; and level of consciousness [3]. Other important assessments include HbA1c, complete blood count, and the establishment of a second IV line. Because DKA is more prevalent in patients with type 1 diabetes, blood should be obtained for the following diabetes-associated autoantibodies: insulin antibody, islet antigen-2 antibody, glutamic acid decarboxylase antibody, and zinc transporter 8 antibody [4].

Fluid Therapy

The diagnosis of DKA is made based on the biochemical criteria listed above. Fluid replacement should be initiated upon the suspicion of DKA as the first goal of therapy is to correct DKA-associated dehydration [5]. Fluid therapy should be initiated before insulin therapy. A fluid bolus of 10–20 mL/kg body weight using 0.9% sodium chloride should be administered over 30–60 min [3]. In patients who are in shock, fluid bolus should be administered over 5–20 min and repeated if necessary. However, shock is relatively uncommon in DKA due to the osmotic effect of the hyperglycemia. The presence of shock in a patient with DKA suggests severe fluid deficit with the possibility of sepsis [3].

Once the diagnosis of DKA has been established and the patient has received intravenous fluid for volume expansion, insulin therapy could be initiated using an insulin infusion protocol [3]. Regular insulin should be prepared in normal saline to a final concentration of 1 unit/mL [5]. It is recommended that about 20 mL of the constituted insulin solution be flushed through tubing to saturate binding sites [6]. Following the flushing, insulin drip should be administered at an infusion rate of 0.05–0.1 unit/kg/h [3]. This rate can be adjusted in patients who are very sensitive to insulin to ensure a glucose lowering rate of about 100 mg/dL (5.5 mmol/L) per hour [3, 5].

The components of fluid requirement for the management of DKA include replacement of fluid deficits and maintenance fluid [5]. In general, a total fluid deficit of 10% is assumed in DKA such that the maintenance fluid administration is initiated at a rate calculated to replace the patient's fluid deficit over a 48-h period [3]. However, some studies have shown that there is no difference in outcome between the slower (classical) or faster fluid replacement protocols [7, 8]. In general, the total fluid volume, excluding insulin, should not exceed 4 times the calculated maintenance fluid volume [9]. A practical way to deliver both the deficit and maintenance fluid is to provide twice the maintenance fluid volume based on the Holliday-Segar Calculation as follows: 100 mL/kg for the first 10 kg, 50 mL/kg for the second 10 kg, and 20 mL/kg for the remainder of the body weight in kilograms [10]. The preferred tonicity of maintenance fluids is 0.9% sodium chloride [5]. One half normal saline solution, that is, 0.45% sodium chloride, can be considered for patients who present with or develop hypernatremia or hyperchloremia [3].

Glucose Management

The goal of blood glucose management is to safely correct the hyperglycemia without inducing complications arising from an overly aggressive glucose lowering approach [3]. This is achieved by using the “two bag method” or the “two bag system.” In this approach, two intravenous fluid bags containing identical fluids with electrolytes are run simultaneously into a single IV line, with one bag containing 0% dextrose and the other containing 10% dextrose. The rates of the two intravenous fluid bags are adjusted based on the rate of decrease in serum glucose

concentration [11]. The combined infusion rates from both IV fluid bags should be equal to 1.5–2 times the calculated fluid maintenance volume. Dextrose containing IV fluids should be added when serum glucose concentration drops to <300 mg/dL (16.7 mmol/L) [11]. Blood glucose concentrations should be monitored frequently and the rates of dextrose-containing fluids and non-dextrose-containing fluids adjusted accordingly. We present the protocol for the two-bag infusion system that is used in our institution, Northwell Health, Cohen Children's Medical Center, New York, in Table 25.1 below. Several variations of this two-bag system protocol may be in use at other institutions; thus, the glycemic cutoffs for intravenous fluid titration may vary across institutions.

If serum glucose concentration cannot be maintained above 180 mg/dL (10 mmol/L) using D10W, then a higher dextrose containing fluid such as D20W can be considered. However, this will require the placement of a central line for the infusion. In this situation, the dextrose titration should be done at a slower rate to avoid large fluctuations in serum glucose level. This is shown below in Table 25.2.

Electrolyte Management

Potassium should be added to the intravenous fluids after the patient has urinated, and the serum potassium level is ≤ 5.5 mmol/L [3, 5]. The general rule is to add 40 mEq/L of potassium to the intravenous fluids as follows: 20 mEq/L as potassium acetate and 20 mEq/L as potassium phosphate (equivalent to 13.6 mmol/L). The phosphate in potassium phosphate is usually sufficient to replace any deficit [5]. For children presenting with a potassium level <3.5 mmol/L, insulin replacement should be deferred (as insulin acts to drive potassium ions into the cells) and a potassium bolus given first, not to exceed 0.5 mmol/kg/h, with cardiac monitoring. Insulin replacement is then initiated when normokalemia is assured [3].

Bicarbonate is no longer recommended in the treatment of uncomplicated DKA. This is because the administration of insulin stops lipolysis and the synthesis of ketoacids, while promoting the metabolism of ketoacids and the regeneration of bicarbonate [12]. However, bicarbonate may be used at a dose of 0.5–1 mEq/kg

Table 25.1 Approach to maintenance fluid replacement in DKA using the two-bag infusion system containing 0% and 10% dextrose solution

| Serum glucose | Intravenous fluid without dextrose | Intravenous fluid with dextrose (D10) |
|----------------------------------|------------------------------------|---------------------------------------|
| <225 mg/dL (12.5 mmol/L) | Off | 100% of total fluid |
| 225–250 mg/dL (12.5–13.9 mmol/L) | 25% of total fluid | 75% of total fluid |
| 251–275 mg/dL (13.9–15.3 mmol/L) | 50% of total fluid | 50% of total fluid |
| 276–300 mg/dL (15.3–16.7 mmol/L) | 75% of total fluid | 25% of total fluid |
| >300 mg/dL (16.7 mmol/L) | 100% of total fluid | Off |

Table 25.2 Approach to maintenance fluid replacement in DKA using the two-bag infusion system containing 0% and 20% dextrose solution

| Serum glucose | Intravenous fluid without dextrose | Intravenous fluid with dextrose (D20) |
|----------------------------------|------------------------------------|---------------------------------------|
| <180 mg/dL (10 mmol/L) | Off | 100% of total fluid |
| 180–200 mg/dL (10–11.1 mmol/L) | 15% of total fluid | 85% of total fluid |
| 201–220 mg/dL (11.2–12.2 mmol/L) | 30% of total fluid | 70% of total fluid |
| 221–240 mg/dL (12.3–13.3 mmol/L) | 45% of total fluid | 55% of total fluid |
| 241–260 mg/dL (13.4–14.4 mmol/L) | 60% of total fluid | 40% of total fluid |
| 261–300 mg/dL (14.5–16.7 mmol/L) | 75% of total fluid | 25% of total fluid |
| >300 mg/dL (16.7 mmol/L) | 100% of total fluid | Off |

intravenously for the management of severe hyperkalemia, or if arterial pH is <7.0 with associated impaired cardiac contractility and vascular tone, and diminished central nervous system status [3].

Vital Signs and Neurological Assessments

Vital signs and neurological assessments should be obtained every hour, or more frequently if the patient is unstable. Particular attention should be paid to signs and symptoms of increased intracranial pressure such as headaches, unequal pupils, and altered mental status or decreased level of consciousness.

Glucose levels should be monitored hourly to ensure a glucose lowering rate of 100 mg/dL (5.5 mmol/L) per hour. When glucose levels are stable, the monitoring could be extended to once every 2 h. Venous blood gas with electrolytes should be monitored hourly. Comprehensive metabolic panel should be checked every 6 h [3].

Cerebral Edema

Cerebral edema is a potentially life-threatening complication of DKA. It can be heralded by complaints of headache or decreased level of consciousness by the patient. Strategies for managing cerebral edema include elevating the head of the bed to decrease intracranial pressure, decreasing the rate of fluid therapy, and administering a hyperosmolar agent. Therapeutic options include the administration of mannitol, 0.25–1 g/kg IV over 20–30 min, or the infusion of 3% sodium chloride, 5–10 mL/kg IV over 30 min. Pediatric intensive care unit, neurology, and anesthesia colleagues should be contacted immediately for help with further management [3].

In general, DKA is resolved when the pH increases to >7.3 and the anion gap normalizes. This is when the patient should be transitioned to subcutaneous insulin delivery. The insulin drip should be discontinued at mealtime, 20–30 min after receiving a short-acting insulin injection for blood sugar correction and carbohydrate coverage [3]. Long-acting insulin should be given 2 h before the discontinuation of the insulin drip to ensure a continuous basal insulin delivery and the prevention of relapse into DKA [13]. This is generally well tolerated and may lead to faster resolution of DKA without increasing the risk of hypoglycemia [14]; however, one study found an association with more frequent hypokalemia [15].

Hyperglycemic Hyperosmolar Syndrome (HHS)

A second life-threatening manifestation of new onset DM is the hyperglycemic hyperosmolar state or syndrome (HHS). HHS is a relatively uncommon presentation of insulinopenia but is associated with a high mortality rate of 15–20% or greater in adults [16]. The incidence of HHS in the pediatric population, although less frequent than the incidence of DKA, is on the rise [17, 18]. Patients with HHS present with significant hyperglycemia and hyperosmolarity but with absent or only mild ketosis. The presentation is often marked by a gradual onset of polydipsia and polyuria such that the symptoms go mostly unrecognized resulting in extreme dehydration and electrolyte losses by the time patients seek medical attention [19]. The diagnosis of HHS is established by the following criteria [3]: plasma glucose concentration of >600 mg/dL (33.3 mmol/L); venous pH of >7.25 ; arterial pH of >7.30 ; serum bicarbonate of >15 mmol/L; mild ketonuria, absent to mild ketonemia; and an effective serum osmolality of >320 mOsm/kg. Additional criteria include altered level of consciousness, as well as seizures in approximately 50% of children [3].

Similar to the treatment of DKA, the first step in the management of HHS is intravenous hydration [19]. However, the major difference is that in HHS, a more aggressive replacement of intravascular volume is required to avoid vascular collapse [19]. This is because as serum osmolality begins to decrease during treatment, water moves out of the intravascular space to the extravascular space [3]. This water shift and the concurrent osmotic diuresis from extreme hyperglycemia could lead to a rapid decreased intravascular volume [3]. Therefore, it is recommended to initiate fluid therapy with a normal saline bolus of ≥ 20 mL/kg of isotonic saline (0.9% NaCl). Additional boluses may be given rapidly to restore peripheral perfusion. When switching to maintenance fluids, a volume deficit of 12–15% of a patient's body weight should be assumed, and the infusion rate should be set to replace the deficit over 24–48 h. It is also recommended to replace urinary fluid losses during the treatment of HHS [20]. Either 0.45 or 0.9% saline solution may be used. The 0.45% saline solution is similar to the urine sodium concentration during osmotic diuresis; however, 0.9% saline solution can be considered for replacement of urinary losses where there are concerns about adequate circulatory volume [19]. It is prudent to place a foley urinary catheter to ensure a careful monitoring of fluid

balance. A central venous pressure monitoring device should be considered if there is no urine output following two to three intravenous fluid boluses [21].

The initiation of intravenous fluid administration often leads to an initial rapid decline in serum glucose concentration [19]. This is then followed by a slower rate of decline. When the rate of decline reaches <50 mg/dL/h (2.8 mmol/L/h), insulin administration should be initiated by continuous infusion, at a rate of 0.025–0.05 units/kg/h [19]. This dose may be adjusted to permit a controlled decrease in serum glucose at a rate of 50–75 mg/dL per hour [19]. In general, there is minimal acidosis in HHS, and this acidosis corrects readily with low insulin infusion rate [3].

HHS is often associated with higher losses in potassium, phosphate, and magnesium than DKA [3, 19]. Therefore, electrolyte deficits should be corrected accordingly. Potassium replacement should be added to the intravenous fluids as 40 mmol/L when adequate renal function is established, and the serum potassium concentration is within the normal range [3]. Phosphate replacement is accomplished with an intravenous solution containing a 50:50 mix of potassium phosphate and another potassium salt such as potassium chloride or potassium acetate [19]. Magnesium replacement can be considered in a patient with severe hypomagnesemia and hypocalcemia, at a starting dose of 25–50 mg/kg per dose for three to four doses given every 4–6 h [19]. The use of bicarbonate therapy is contraindicated in HHS as it increases the risk of hypokalemia and impair tissue oxygen delivery [3]. Serum electrolytes, including potassium, calcium, magnesium, and phosphate, should be monitored every 2–4 h.

Patient Education

Patient Education for Children with New-Onset Diabetes Mellitus

Full diabetes education session for the patient and their family members starts after the resolution of DKA or HHS. The education session is also offered to children and adolescents with new-onset DM who did not present in either DKA or HHS. These sessions involve close interaction between the diabetes team and the patient and their family. As shown in Fig. 25.1, the diabetes team or caregivers include physicians or other providers, certified diabetes care and education specialists, nutritionists, social workers, and, in some cases, a psychologist. The diabetes team instructs the patient and their family on the basic skills of diabetes management such as insulin dose calculation and administration, glucagon administration for hypoglycemia, techniques of blood glucose monitoring, carbohydrate counting, routine management of hypo- or hyperglycemia, and the approaches to the management of diabetes during an acute illness.

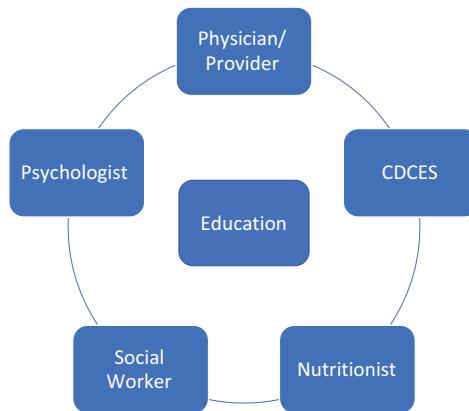


Fig. 25.1 Key professionals and areas of coverage in pediatric diabetes education. The physician or provider focuses their teaching on the diagnosis, pathophysiology, and DM classification. The Certified Diabetes Care and Education Specialist (CDCES) focuses on the day-to-day management of diabetes, including insulin administration, dose calculation, glucose monitoring, hypo- and hyperglycemia management, and diabetes management during illness. The nutritionist focuses on healthy eating, carbohydrate counting, and mealtime routines. The social worker ensures access to resources. The psychologist explores patient's feelings around diagnosis, including blame, guilt, grief, anger, and frustration

Patient Re-education for Children with Established Diabetes Mellitus

Patients with established DM may develop DKA and HHS from various factors such as intercurrent illnesses, nonadherence to insulin administration schedule, malfunction of insulin delivery devices, or the use of expired insulin. The protocol for the ED and inpatient management is the same as for patients with new onset DM who present in DKA or HHS. Additional management includes identifying the precipitating cause of the DKA or HHS, and addressing it, to prevent recurrences. The diabetes team should review the patient's insulin regimen to ensure adequate insulin dosages, as well as develop a patient-specific plan for cases of nonadherence. This plan may require increased supervision by an adult or setting alarms or timers for insulin administration.

Approaches to the Management of Either Hyperglycemia or DM During Hospitalizations for Other Reasons

Children with Critical Illnesses in an Intensive Care Setting

Stress-induced hyperglycemia is a common complication in critically ill children with or without diabetes mellitus [22]. Hyperglycemia leads to serious cardiovascular morbidity and delays wound healing [22, 23]. This hyperglycemic response may

be more severe in critically ill children with DM with greater propensity for hyperglycemia [24].

However, the concerns for hyperglycemia should be placed in perspective with the risk for hypoglycemia, which is equally life-threatening. Recent studies in children found no advantages in the short or long term from the use of intensive insulin therapy to maintain tight glycemic control in critically ill children [25–27]. In fact, studies show that patients in the lower-glycemic target group (80–110 mg/dL, 4.4–6.1 mmol/L) had higher rates of health care-associated infections than those in the higher-target group (150–180 mg/dL, 8.3–10.0 nmol/L). The lower-glycemic target group also had higher rates of severe hypoglycemia with blood glucose reading of <40 m/dL (<2.2 nmol/L) [26]. The Control of Hyperglycemia in Pediatric Intensive Care (ChiP) trial, which studied 1369 children in 16 intensive care units, also found no difference in mortality and ventilator free days between the groups but reported *increased* episodic severe hypoglycemia in the tight-glycemic-control group compared to the conventional-glycemic-control group [27]. Therefore, we recommend a target blood glucose of 140–180 mg/dL [4].

Though these studies did not specifically investigate the outcomes in children with DM in intensive care units, their findings provide sufficient evidence against the recommendation of tight glycemic control in critically ill children with diabetes mellitus.

However, frequent glucose monitoring is important to prevent extreme glycemic excursions. In most cases, the patient's home insulin regimen can be continued with modifications made to reflect the patient's status while in the hospital.

Inpatient Management of Children with DM, but Without Critical Illnesses

The maintenance of optimal glycemic control in the inpatient setting is crucial for the promotion of overall health and other health-related issues such as wound healing [23]. Attention must be paid to the monitoring of carbohydrate intake through carbohydrate counting in most cases. In some cases, a nutritional consult may be necessary to refresh the family's understanding of the patient's diet plan. Patients should avoid high glycemic index foods such as juices and syrups [4]. Finger-stick blood glucose levels should be monitored before each meal and at bedtime. In most cases, the patient's home insulin regimen should be adequate to maintain normal glucose levels in the hospital setting. Providers should understand that hospitalization may cause glycemic excursions that are not experienced at home. Some of the common causes of these excursions are intercurrent infections, the use of antibiotics, sedentary mode of living and activity levels in hospital, and changes in diet. Stable patients who are already using a continuous glucose monitor (CGM) for glucose monitoring can continue to use the device. Several studies in adult patients with diabetes mellitus have confirmed the safety and efficacy of CGM in the

hospital setting [28–30]. The use of CGM ensures accurate and continuous monitoring of glucose levels with reduced risk for severe hypo- or hyperglycemia while decreasing the frequency of finger-stick testing, which is important in young children [38]. Given that more studies are needed to test feasibility and limitations of CGM in hospitalized children, we recommend continued intermittent finger-stick checks throughout hospitalization [28]. If the correlation between finger stick and CGM is deemed to be consistent and there is significant burden to a child, finger sticks can be decreased at the discretion of the pediatric endocrinologist.

Pre-surgical Management of Type 1 Diabetes

Pre-surgical Preparations

Achieving optimal preoperative and intraoperative glycemic control in children with DM is challenging and requires a multidisciplinary team approach [31, 32].

If possible, surgical procedures and surgeries should be planned at experienced medical centers with the expertise and staff to treat children with DM [33]. Patients with diabetes should be scheduled as the first case of the day to decrease fasting times [31, 32, 34]. Many guidelines recommend that these patients be admitted to the hospital if they will receive general anesthesia [33, 34].

Pre-surgical assessment of glycemic control, serum electrolyte, and serum or urine ketones is critical to ensure the safety of children undergoing elective surgery. This should be done several days before the date of surgery to confirm that the patient is metabolically stable with no evidence of diabetic ketoacidosis [32, 34]. Though there is no pediatric consensus on a cutoff HbA1c value to trigger a delay of surgery, adult literature suggests that HbA1c of >8% may warrant surgical delay or pre-admission to optimize glycemic control [34, 35].

Glucose Management on the Day of Surgery

On the day of the surgical procedure, it is important to maintain euglycemia without the need for additional caloric intake while the patient is on *nil per os* (NPO) protocol in the hours leading up to the procedure. For this reason, most centers will recommend considering a decrease of the overnight basal insulin dose or long-acting insulin dose by 10–20% depending on the patient’s regimen. Since the patient is not eating any food, no short-acting insulin injection is needed on the day of the surgery, except in the event of persistent hyperglycemia. It is crucial not to withhold basal insulin administration entirely to avoid the development of DKA [32, 33].

Prior to any procedure, the full surgical team should have a good understanding of a patient’s insulin regimen including their glucose targets, insulin-to-carbohydrate ratio, and insulin sensitivity factors [34]. The recommended target glucose range before surgical procedures is 90–180 mg/dL (5–10 mmol/L) [32, 33].

For most procedures, the patient can receive a maintenance infusion of normal saline or other non-dextrose containing fluids [32]. Blood glucose levels should be monitored every hour [32–34], or more frequently, every 30 min for acute changes in blood glucose levels, or every 15 min to monitor for hypoglycemia if any of the glucose levels is <80 mg/dL (4.4 nmol/L) [31].

While NPO, we recommend treatment of hypoglycemia of <70 mg/dL (<3.9 nmol/L) with a bolus administration of D10 solution, 2 mL/kg, followed by maintenance D10% IV fluids, and rechecking blood the glucose level after 15 min. This should be repeated as needed for instances of persistent hypoglycemia [31]. Insulin dose adjustment might be necessary in this scenario to prevent hyperglycemia [33]. If blood glucose levels are >250 mg/dL, consider administering subcutaneous rapid-acting insulin using the patient's home correction factor or if not known, then use 5–10% of the patient's usual total daily dose (TDD) as the correction insulin dose [33]. In this case, urine or blood ketone concentrations should be measured, and intravenous insulin infusion should be considered if there is significant ketosis [33].

Continuous Glucose Monitoring in the Operating Room Setting

Continuous glucose monitoring (CGM) has revolutionized pediatric diabetes care, providing fairly accurate blood glucose data every 5 min including trend predictions for future hypoglycemia or hyperglycemia [33, 36]. However, the reliability of the CGM has not been fully evaluated in the perioperative setting. Given the potential impact of significant hypoperfusion and hypothermia on glucose readings, more clinical data are required to better understand CGM accuracy in the “real-world” surgical setting. Additionally, some medications such as acetaminophen can impact the glucose data from some CGM devices [37]. Furthermore, inadvertent positioning of the CGM on compressed body areas could lead to false reading of hypoglycemia, a phenomenon known as compression artifact. For these reasons, CGM should be used with caution and used to trend blood sugars but should not be used alone to make final clinical decisions [33, 34]. Current guidelines from the International Society for Pediatric and Adolescent Diabetes (ISPAD) support the option to use CGM devices with caution, preferably under research protocols and with additional glucose assessments [33]. This approach may be useful in shorter procedures.

Continuous Subcutaneous Insulin Infusion (CSII) in the Operating Room

Continuous subcutaneous insulin infusion (CSII), or insulin pump, can be used safely throughout the course of many surgical procedures provided the anesthesiologist is comfortable with its use. If the anesthesia team is not accustomed to an insulin pump, it is recommended that the pump be removed, and an intravenous continuous insulin infusion (insulin drip) be started in its place [33]. Basal rates

should be continued based on home regimen for shorter procedures and can be suspended for no more than 30 min for the correction of acute episodes of hypoglycemia. If there is concern for hypoglycemia, consideration should be given to decrease the basal rate by 20% at 3 am on the morning of the procedure [33]. Bolus insulin doses are usually not necessary unless there is significant hyperglycemia or ketone production [33].

Adjustments for Minor Surgery/Procedures

The use of CSII is well suited for short procedures, defined as lasting <2 h and when rapid recovery is anticipated, such as endoscopic biopsies, MRIs, or other imaging studies. Blood sugar levels can likely be maintained on basal insulin alone with no need for additional doses of short-acting insulin during the procedure. For these procedures, CSII can be used if its position does not interfere with the surgical field [33].

Postoperative Care

The patient's insulin regimen can be fully re-started with both the short- and long-acting insulins when the patient is awake and ready to resume baseline oral intake of food and drinks [32].

Pre-surgical Management for Children with Type 2 Diabetes

The rising prevalence of childhood obesity has also led to a rising trend for type 2 diabetes in the pediatric population [33]. It is therefore essential to maintain surgical guidelines specific to this population.

For patients receiving metformin therapy, it is generally recommended to hold the metformin 24 h prior to the operation in long-duration surgeries to help prevent the risk of lactic acidosis [33]. For shorter procedures, metformin may be held only on the day of the procedure. In all cases, metformin should be withheld for 48 h following the completion of the surgery for the confirmation of optimal renal function. Similarly, sulfonylureas, thiazolidinedione, **dipeptidyl peptidase IV (DPP IV) Inhibitors, and glucagon-like peptide-1 receptor agonists (GLP1RA)** should all be discontinued on the day of surgery and may be restarted as soon as oral intake is fully re-established following surgery [33]. The need to possibly hold GLP1RA for longer periods before surgery due to delayed gastric emptying will need to be clarified in the pediatric population. For patients with T2DM using insulin therapy, the guidelines presented for patients with T1DM should be followed.

Conclusions

Children and adolescents with new-onset or established DM require special care when they are admitted to the hospital. In this chapter, we have detailed the approaches to each aspect of the inpatient care for this pediatric population to ensure optimal outcome for these patients. Specific aspects of management encompass close monitoring of the patient including mental status evaluation when indicated, adequate planning before elective surgical procedures, precise fluid management, optimal insulin therapy, and electrolyte monitoring and replacement.

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Part IV

Inpatient Diabetes and Nutrition

Chapter 26

Diabetes and Oral Nutrition for Hospitalized Patients



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Introduction

Malnutrition is associated with unfavorable clinical outcomes among hospitalized patients. It leads to decreased tolerance of treatment, poor prognosis, increased rates of hospital-acquired infections, poor wound healing, and longer lengths of hospital stay [1]. The prevalence of malnutrition ranges from 38 to 78% in the intensive care unit (ICU) [2]. Unfortunately, it is often underdiagnosed and undertreated [3]. The primary purpose of inpatient medical nutrition therapy (MNT) is to provide adequate calories to meet metabolic demands and to optimize glycemic control. Nutritional assessment of diet quality for all hospitalized patients is crucial to optimize metabolic and nutritional status that may in turn improve hospital outcomes.

The MNT plays an essential role in inpatient glycemic management in patients with diabetes mellitus and hyperglycemia. Inpatient hyperglycemia is a stronger risk factor than diabetes for an increased risk of adverse in-hospital outcomes such as hospital complications, increased length of stay, and mortality [4, 5]. In the COVID-19 pandemic context, among critically ill COVID-19 patients, early-onset hyperglycemia was associated with significantly increased mortality and higher levels of inflammatory markers [6].

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Nutritional management sufficient to achieve optimal glycemic control during hospitalization is challenging. Both hyperglycemia and hospital-acquired hypoglycemia are serious adverse events. Current evidence-based clinical guidelines emphasize the need for proper timing of point of care blood glucose measurements, mealtime insulin administration, and meal delivery to reduce the incidence of both hypoglycemia and hyperglycemia [7]. Monitoring and improving the timing of these interventions are crucial steps in the safe and effective care of patients with diabetes [7].

The collaboration of multidisciplinary teams including dietary and education departments, bedside nurses, and medical practitioners is the key to achieve successful outcomes in persons with diabetes [8].

General Approach to Oral Medical Nutrition Therapy

Oral nutrition is the optimal preferred method for receiving nutrition for all hospitalized patients. Currently, a carbohydrate consistent diet is the recommended choice for hospitalized patients with diabetes. Carbohydrates are known to have the greatest effect on blood glucose, and thus, the goal of a carbohydrate consistent diet is to minimize the effect of food on the risk of hyperglycemia. A standard diet includes 50–67% grams of carbohydrates, translating to 250–335 g of carbohydrates in a 2000-calorie diet. For patients with diabetes, a consistent carbohydrate diet is recommended; this includes 33–47% grams of carbohydrates, consisting of 160–235 g of carbohydrates per day for a 2000-calorie diet [1]. Typically, breakfast would include 45–75 g of carbohydrates, and lunch and dinner each include 60–75 g of carbohydrates. Consistency attempts to control glycemic levels for patients with diabetes and allows the practitioner to adequately evaluate the efficacy of medical therapy with insulin.

However, there have been other studies demonstrating that a diet with more freedom of choice that does not limit carbohydrate consistency may lead to meeting nutritional goals and less food waste [9]. It is understood that some patients, especially the elderly, may feel restricted when choosing food based on calorie or carbohydrate restriction and may in turn cause decreased appetite, decreased food intake, and weight loss. Also, changes in carbohydrate intake that vary day to day will inevitably make glycemic control more challenging [9]. The dietary approach with such freedom of choice has not yet been widely accepted nor implemented in the inpatient setting [9].

In recent times, some hospitals have changed from carbohydrate consistent diets to “meals on demand”; however, for patients with diabetes on insulin, this results in impaired glycemic control due to the variability in carbohydrate content and lack of coordination in glucose monitoring and insulin administration. Several approaches have been suggested to circumvent dissatisfaction and at the same time achieve adequate glycemic control. Recommended suggestions include letting patients have control over their meal orders and nursing staff being notified so as to obtain

finger-stick blood glucose and promptly administer insulin based on carbohydrate intake to achieve adequate glycemic control [9].

The importance of nutrition equates to the importance of having a dietary consultant involved in the nutritional care of a patient to create a comprehensive plan of metabolic optimization. Evaluation of dietary needs and discussion with the patient is vital in meeting nutritional goals. This, however, presents a challenge because the volume of hospitalized persons with diabetes typically outnumbers available nutritionists in the inpatient setting. Even with a qualified nutritionist involved in patient care, managing hyperglycemia inpatient is not without its obstacles. Multiple factors exist to adequate management, including on-time meal and insulin delivery, multiple daily monitoring of point-of-care-glucose values, patients away from their room, variations in appetite due to underlying illness, and nurse availability [10]. Rapid-acting insulin should be given to the patient 15 min prior to eating. This can be challenging since distribution of medication and delivery of meal tray may not line up appropriately. Various institutions have addressed these issues with direct messaging to the nursing staff that the food trays have arrived with intent that insulin can be distributed in a timely manner [9]. Another method includes a nurse-driven process that coordinates glucose delivery, meal delivery, and insulin administration [9]. Other challenges can also exist such as patient preference of the hospital diet, family support, compliance with medications, and understanding the importance of glycemic control [11]. For example, as a show of support, families will often bring in food from outside for the patients. However, the meals or snacks may not be in line with the recommended diet. For that reason, it is suggested that during patient education, family and patients should participate, if possible, in carbohydrate counting [12].

Patient-specific factors should be taken into consideration when deciding on a diet with the goal of reducing hyperglycemia. Patients receiving steroid therapy are at a higher risk of hyperglycemia. It is important to note that these patients should not be exposed to further caloric restriction to help hyperglycemia management as this may put them at a higher risk for malnutrition [12]. In times of acute illness, nutrition should be optimized as opposed to a calorie restricted diet, as the latter could lead to malnutrition and worsening of the patient's condition. The geriatric patients frequently have dysphagia, and for that reason, diets are often liberalized. It is still important to consider the source of hyperglycemia within carbohydrate values of protein shakes and excess sugar that may come from methods of medication administration, for example, medications crushed in applesauce or IV medications given in a dextrose solution [13]. Glycemic optimization has been shown to be of the utmost importance for total health management in the inpatient setting; however, there are no studies that tested the effects of different oral nutrition approaches of glycemic and clinical outcomes in persons with diabetes. Ketogenic diets have been found to reduce caloric intake and body weight ultimately affecting glycemic control; however, no studies have assessed its safety and benefits in hospitalized patients, and therefore, they are not recommended for hospitalized patients at this time [14, 15]. Low-calorie diets are generally not recommended in hospitalized patients with diabetes who are obese as this can promote malnutrition [12, 16].

Liquid Diets

Patients' clinical scenarios may require alternative diets such as a liquid diet, which is typically temporary and ultimately advanced to a solid diet. The focus for patients with diabetes in the hospital should be the same as for non-diabetes patients—they should be provided with adequate calories to meet their metabolic demands and to optimize glycemic control [17]. Although these diets are temporary, adjustments to fat, carbohydrate, proteins, and micronutrient intake should be made [11]. As per European Society for Clinical Nutrition and Metabolism guidelines, inpatients with multiple comorbidities should have at least 75% of calculated energy and protein requirements be achieved in order to reduce risk of adverse outcomes [18].

Nutritional risk should also be evaluated and taken into consideration, as a liquid diet can last longer than just a temporary measure. Patients at high nutritional risk should be given a hospital-based diet enriched with protein and energy. Patients with no or low risk should have a standard diet but be reevaluated after 5 days [12, 13, 16, 19–21]. Persons with type 1 and type 2 diabetes should be given the standard diet, which should be determined based on current glycemic control, nutritional risk, and other medical comorbidities. If a patient's blood glucose levels are suboptimal in the hospital, food intake should not be reduced, but rather optimization of insulin therapy should be attempted. Reduction of food intake puts these patients at high risk of malnutrition [13, 21, 22]. Table 26.1 outlines the ideal nutritional targets per day for the general population.

Table 26.2 provides a list of oral nutritional drinks that can be used to supplement a patient's caloric intake. A large Cochrane systematic review of 24 studies involving over 6000 patients who are 65 years or older at risk for malnutrition also showed fewer complications, such as pressure sores, deep vein thrombosis, respiratory and urinary infections, among those who received oral nutrition supplements, compared to those who received routine care [23]. High-protein nutrition supplements have shown to reduce ulcers by 25% compared to standard care [23]. A meta-analysis of 11 studies with nearly 2000 patients showed a 19% mortality rate in those receiving oral nutrition supplements versus 25% in those who did not receive supplements [24]. Glucerna is beneficial in patients with diabetes due to its low-calorie and low-carbohydrate content. A study by González-Ortiz showed that a single

Table 26.1 Nutrition targets per day for the general population

| Nutrient | Standard diet | Hospital diet |
|-------------------|---------------|---------------|
| Protein (g/kg BW) | 0.8–1.0 | 1.2–2.0 |
| Carbohydrate (E%) | 50–60 | 45–50 |
| Lipid (E%) | 30–35 | 35–40 |
| Protein (E%) | 15–20 | 20–25 |

Index: g/kg BW—Grams/kilogram of body weight

E%: Percent of total energy

Table 26.2 Nutritional supplements

| | Size | Protein | Carbohydrates | Calories | Fat |
|----------------------|------|---------|---------------|----------|------|
| Boost (vanilla) | 8 oz | 10 g | 37 g | 240 | 6 g |
| Boost high protein | 8 oz | 20 g | 28 g | 250 | 6 g |
| Ensure original | 8 oz | 9 g | 32 g | 220 | 6 g |
| Ensure clear (apple) | 8 oz | 8 g | 52 g | 240 | 0 g |
| Ensure high protein | 8 oz | 16 g | 19 g | 160 | 2 g |
| Glucerna | 8 oz | 10 g | 16 g | 180 | 9 g |
| Nepro | 8 oz | 19 g | 38 g | 420 | 23 g |

administration of Glucerna decreased postprandial glucose and insulin secretion and increased insulin sensitivity [25]. Another study by León-Sanz showed that Glucerna had a neutral effect on glycemic control and lipid metabolism in patients with diabetes compared to high-carbohydrate formulas [26].

Patients requiring clear or full liquid diet should receive 160–235 g of carbohydrate per day in equally divided amounts at meal and snack times. Liquids should not be sugar free. Patients require carbohydrates and calories, and sugar-free liquids do not meet these nutritional needs.

Some of the disease states in which liquid diets are initiated include postoperative surgical patients, pancreatitis, gastroenteritis, and disease states causing dysphagia. In most cases, food intake should be initiated as quickly as possible with progression to solid foods [19, 20]. It was once believed that enteral nutrition should not be initiated until bowel function has returned; however, there is increasing evidence that early feeding results in enhanced wound healing and decrease in morbidity and mortality associated with wound infection, decrease in mortality of patients with sepsis, decreased weight loss, and improvement in protein kinetics [20]. It is very difficult to provide adequate nutrition with only a liquid diet, and advancement to a regular diet is recommended as soon as clinically indicated [20]. It can also be beneficial to seek a consultation from a speech therapist to adequately advance diet when the patient is ready, as well as to request nutritionist involvement to assess patients' daily caloric needs. Patients can be very medically and nutritionally complex, and assistance from a multidisciplinary team that includes a nutritionist as well as a speech therapist can improve their clinical course. For example, patients with diabetes who are admitted to hospital for renal failure may be put on a very restrictive diet and may have very limited nutritional options. These patients would benefit from a multidisciplinary approach in order to provide the best nutritional recommendations. Patients should have close follow-up with these services and primary care physicians on discharge from the hospital.

Conclusion

Medical nutrition therapy is an essential component of optimal inpatient glycemic control in patients with diabetes. Optimizing nutritional status in the hospital leads to increased treatment tolerance and decreased rates of hospital-acquired infections. No randomized controlled studies have compared different nutritional strategies in the hospital, but the use of carbohydrate consistent meal planning systems has been effective in facilitating glycemic control in the hospital setting. Over the last several years, many hospitals transitioned from a consistent carbohydrate diet to “meals on demand” system. This system gives patients flexibility in their mealtimes and food selections. To achieve effective glycemic control, comprehensive nutritional care plans should be designed by professional dietitians knowledgeable in glycemic management.

Liquid diet is most frequently used as the initial postoperative meal. Although generally well tolerated, liquid diets have potential risks that fail to provide adequate nutrients to postsurgical patients. In most cases, advancing the diet from clear liquid to full liquid to solid foods should happen as quickly as possible. Future studies are needed to compare the safety and beneficial effects of different oral nutritional strategies in the hospital setting.

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Chapter 27

Diabetes and Enteral Nutrition in the Hospital Setting



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Introduction and Background

Malnutrition is a common consequence of illness, especially in the inpatient setting. Nutritional support is defined as methods to improve or maintain nutritional intake and includes three types: oral nutrition support with fortified foods, enteral nutrition delivered directly to the gut, and parenteral nutrition that is delivered intravenously [1]. This chapter will cover enteral nutrition, and parenteral nutrition will be covered in the next chapter (Chap. 28). Enteral nutrition (EN, also known as “tube feeding”)-associated hyperglycemia is a form of stress/hospital hyperglycemia. There are more than 30 million hospitalizations per year in the United States [2], and approximately 0.5% of hospitalized patients receive EN [3]. Up to 30% of hospitalized patients with or without diabetes are estimated to develop hyperglycemia while on EN [4], but contemporary data are lacking. A recent systematic review and meta-analysis of randomized controlled trials concluded that the use of EN as compared with parenteral nutrition has no effect on mortality but may decrease hospital infections and intensive care unit (ICU) length of stay [5]. However, this finding was not supported by a subsequent Cochrane Database systematic review [6]. Enteral nutrition consists of a nutritional formula that usually contains protein, carbohydrates, fats, vitamins,

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and minerals and is delivered into the stomach or small intestine via a feeding tube such as a nasogastric tube, a Dobhoff tube, a nasojejunal tube, a percutaneous endoscopic gastrostomy (PEG) tube, or a jejunostomy tube [7]. Patients with pre-existing diabetes often require additional glycemic management when receiving EN to achieve glycemic goals.

EN-associated stress hyperglycemia is associated with increased mortality and complications including infections [8]. Guidelines by the leading professional societies including the Endocrine Society [8] and the American Diabetes Association [9] recommend good glycemic control in the hospital setting to achieve optimal clinical outcomes. With the continuous nature of these feedings patients are in effect in a postprandial state and thus these societies, along with the American Society for Parenteral and Enteral Nutrition note that a goal range of 140–180 mg/dL is a reasonable target in hospitalized adult patients with hyperglycemia receiving nutrition support [10].

Patients receiving insulin therapy for EN-associated hyperglycemia are at considerable risk for hypoglycemia because of numerous EN-specific scenarios involving both planned and unplanned interruption of EN. Planned interruptions include nil per os (NPO) status for imaging studies and procedures, extubation trials, administration of medications, and discontinuation of EN to transition to oral intake, while unplanned interruptions include tube blockage, removal of the tube by the patient experiencing discomfort or delirium, EN intolerance leading to emesis, and discontinuation during emergent patient transfer to a higher level of care. In addition, the overall complexity of managing patients receiving EN while trying to increase oral intake can lead to hypoglycemia due to mismatch of insulin with actual intake in the setting of poor appetite, nausea, and emesis.

Randomized controlled trials comparing management strategies for EN-associated hyperglycemia are sparse. An extensive literature search was performed to address this clinical question, and data from three randomized controlled trials and six retrospective studies are outlined and described in the “Clinical Trial Evidence” section of this chapter.

General Principles of Management

Several approaches can be used for glycemic management in hospitalized patients receiving EN. To first define our glucose goals and definition of hypoglycemia in this population, we look to the American Society for Parenteral and Enteral Nutrition (ASPEN). ASPEN reviewed the available evidence comparing tight versus standard glycemic control and its effect on mortality in their 2013 clinical guidelines on nutritional support for adults with hyperglycemia [9]. Overall, they found strong evidence for their recommendation of a target blood glucose of 140–180 mg/dL and for hypoglycemia to be defined as <70 mg/dL in adult hospitalized patients receiving nutritional support. This recommendation is aligned with the notion that patients on nutritional support are often in a postprandial state.

To achieve goal glucose values, there are several considerations including EN schedule, EN composition, choice of insulin regimen, and using dextrose infusions of D10% or D5% when EN is interrupted to prevent hypoglycemia. EN is usually administered on three main schedules: continuously over 24 h, cyclically (usually overnight for between 12–16 h but duration can vary widely), or in boluses (3–5 per day) to mimic meal physiology. Patients can also either be NPO with EN, be on both EN and parenteral nutrition, or be taking PO and receiving supplemental EN. Recently, an additional consideration has come into play as some institutions have introduced protocols to either increase EN rate prior to a scheduled interruption like a procedure or to increase the feeding rate at a “catchup” rate after the scheduled interruption. This further complicates glycemic control, especially in patients with diabetes and those on insulin. Patients can experience further excursions in glucose during the time of the temporary higher EN rates, as well as potentially experiencing hypoglycemia when insulin is increased reactively, but the EN rate drops back down soon after this catchup period.

There are various EN formulations including diabetes-specific formulas (DSF), which focus on decreased carbohydrate content and increased monounsaturated fatty acid content compared to standard enteral formulas. A systematic review and meta-analysis done by Ojo et al. examined randomized control trials (RCTs) that compared DSF to standard formula in patients with type 2 diabetes [11]. All 14 included RCTs showed that DSF was effective in lowering blood glucose parameters compared to standard formula. Some of these parameters were improved glycemic control and lower insulin requirements, shown in eight of the RCTs, and lower postprandial blood glucose levels, shown in four of the RCTs. In practice, we are often limited to what EN formulations a specific hospital carries.

For insulin regimens, there are a wide variety used in practice. The Endocrine Society recently published updated practice guidelines for management of hyperglycemia in hospitalized non-critically ill patients [8]. They acknowledge that there is insufficient evidence to strongly recommend a particular regimen, but they suggest adult patients hospitalized for noncritical illness who are receiving EN with diabetes-specific and nonspecific formulations, receive either NPH-based or basal bolus insulin regimens. These regimens encompass most of those used in practice, including glargine or detemir with aspart or lispro regimens, 70/30 (NPH/regular) every 8 h, and NPH regimens with or without short-acting insulin. The remaining regimens that are used in practice that would not fall under this recommendation are correction only insulin protocols and regular insulin nutritional coverage with or without correction every 6 h.

Clinical Trial Evidence

Evidence for specific glycemic management strategies for hospitalized patients on EN is scant. There are three randomized controlled trials (RCTs) (Table 27.1), five retrospective cohort studies, and one cohort study with retrospective and

Table 27.1 RCTs evaluating insulin regimens for glycemic control in patients receiving EN

| First author | Year | Study design | Sample size | Population | Regimens compared | EN schedule | Results |
|------------------|------|------------------------------|-------------|---|---|-------------|---|
| Korytkowski [20] | 2009 | RCT, parallel, single center | 50 | • Non-critically ill • +/– DM • USA | 1. SC RI correction (+NPH if persistent hyperglycemia) 2. SC gelargine + SC RI correction | N/S | <ul style="list-style-type: none"> • Mean glucose similar between groups (but NPH had to be added to 48% of group 1) • Hypoglycemia did not differ |
| Liu [12] | 2012 | RCT, parallel, single center | 87 | • Critically ill • +/– DM • China | 1. SC RI <-> IV RI infusion if persistent hyperglycemia 2. SC gelargine + SC RI <-> IV RI infusion if persistent hyperglycemia | N/S | <ul style="list-style-type: none"> • Group 1 had lower mean glucose levels (7.58 vs 9.40 mmol/L, $P < 0.05$) • Group 1 had higher % values in target range (49.72% vs. 35.61%, $P < 0.01$) • Group 1 had fewer patients converted to IV RI infusions (9.09% vs. 44.19%, $P < 0.01$) • Hypoglycemia did not differ |
| Yuan [13] | 2015 | RCT, parallel, single center | 212 | • Post-gastrectomy • DM • China | 1. SC N/S insulin correction, target <200 mg/dL 2. IV RI infusion, target 80–110 mg/dL | Continuous | <ul style="list-style-type: none"> • Group 2 had lower mean glucose levels (5.4 vs 9.5 mmol/L, $P < 0.001$) • Group 2 had higher % target blood glucose levels (86.3% vs 72.6%, $P = 0.023$) • Group 2 had lower rates of surgical site infections (4.7% vs 13.2%, $P < 0.030$) • Group 2 had higher rates of severe hypoglycemia (7.5% vs 0.9%, $P = 0.035$) |

EN enteral nutrition; RCT randomized controlled trial; DM diabetes mellitus; SC subcutaneous; RI regular insulin; N/S not specified

prospective arms published that evaluate currently available insulin regimens in this population (the latter are outlined in Table 27.2). Unfortunately, the terminology “sliding scale” is used often to describe rapid-acting, short-acting, and even occasionally intermediate-acting, insulin regimens in this literature, but this is not precise language. Sliding scale does not designate whether a regimen encompasses nutritional coverage only, correction coverage only or a combination of the two. In the discussion that follows, rapid- and short-acting insulin regimens are noted to be nutritional and/or correction coverage if the details were available and no identifiers are used if this was not specified.

Korytkowski et al. randomized 50 patients with hyperglycemia on EN to receive either subcutaneous regular insulin correction every 4–6 h or glargine once daily in addition to regular correction insulin [20]. Throughout the study, NPH insulin was added for persistent hyperglycemia in the regular insulin correction only group, and by the end of the study, 48% of subjects required this addition. The target glucose range was 5.6–10 mmol/L (100–180 mg/dL), and hypoglycemia was defined as <3.9 mmol/L (<70 mg/dL). There were no differences shown between the two groups in mean glucose levels, total daily insulin doses, hypoglycemia, or other adverse events. Liu et al. also evaluated a subcutaneous regular insulin only regimen compared to a glargine and regular insulin regimen [12]. They randomized 87 patients in the ICU to one of these two regimens once the EN reached 50% of the total daily energy requirement. Their target glucose range was 4.4–7.8 mmol/L (80–140 mg/dL). If blood glucose was ≥11.1 mmol/L twice in a row in patients in either group, they were converted to an insulin drip until better glycemic control was achieved and then converted back to their randomized subcutaneous regimen. In the glargine with regular insulin group, mean glucose levels were lower, the percent of glucose values within target range was higher, and less patients in this group were converted to IV insulin throughout the study period. Hypoglycemia, defined as ≤3.3 mmol/L (≤60 mg/dL), did not differ between groups. The third RCT was designed to compare what was the conventional glycemic management at the First Affiliated Hospital of Zhengzhou University (a subcutaneous insulin correction only protocol with a target glucose of <200 mg/dL) to intensive glycemic management in post-gastrectomy patients on continuous EN with known diabetes [13]. The intensive glycemic management arm consisted of a continuous IV regular insulin infusion with a target range of 80–110 mg/dL. The intensive insulin group did achieve lower mean glucose levels, lower rates of severe hyperglycemia, and lower surgical site infection rates but also had higher rates of severe hypoglycemia, defined as ≤2.2 mmol/L (≤40 mg/dL).

Four of the six retrospective cohort studies examined patients on continuous EN. The largest of these studies analyzed 159 patients who were on three different insulin regimens [15]. Patients received either NPH insulin every 4 h, NPH insulin every 6 h, or an aspart insulin regimen. Both NPH groups had lower mean glucose levels and more glucose values in the target range of 80–110 mg/dL than the aspart group did, but the NPH every 4-h group had the most hypoglycemia (definition for hypoglycemia not provided). Hijaze et al. also studied a NPH-based regimen by comparing patients who received NPH three times daily at a starting dose of 0.15 units/kg

Table 27.2 Retrospective studies evaluating insulin regimens for glycemic control in patients receiving EN

| First author | Year | Study design | Sample size | Population | Regimens compared | EN schedule | Results |
|--------------|------|----------------------------|-------------|--|---|-----------------|---|
| Grainer [14] | 2007 | Retrospective cohort study | 52 | <ul style="list-style-type: none"> • Critically ill • DM or fasting BG >200 mg/dL at admission • USA | <ul style="list-style-type: none"> 1. SC N/S insulin 2. SC glargine + SC Lispro nutritional and correction | Bolus every 4 h | <ul style="list-style-type: none"> • Group 2 had lower mean glucose levels (148.9 vs 225.1 mg/dL, $P = 0.0001$) • Group 2 had more time in target range 80–140 mg/dL (48.6% vs 8.3%, $P = 0.01$) • Group 2 had more hypoglycemia (4.14% vs 1.7%, $P = 0.02$) |
| Cook [15] | 2009 | Retrospective cohort study | 159 | <ul style="list-style-type: none"> • All inpatients • +/- DM • USA | <ul style="list-style-type: none"> 1. SC NPH every 4 h 2. SC NPH every 6 h 3. SC Aspart | Continuous | <ul style="list-style-type: none"> • Groups 1 and 2 had similar mean glucose levels (134.7 mg/dL and 133.4 mg/dL) that were lower than group 3 (156.8 mg/dL, $P < 0.001$) • Groups 1 and 2 had similar % BGs in target range (25% and 24%) that were greater than in group 3 (13%, $P < 0.001$) • Group 3 had less hypoglycemia than group 1 (0.7% vs 1.36%, $P = 0.03$), but hypoglycemia did not differ between any group and group 2 |
| Hsia [16] | 2011 | Retrospective cohort study | 22 | <ul style="list-style-type: none"> • Non-critically ill • DM • USA | <ul style="list-style-type: none"> 1. Glargine + Lispro nutritional and correction 2. 70/30 insulin twice daily + Lispro correction 3. 70/30 insulin three times daily + Lispro correction | Continuous | <ul style="list-style-type: none"> • Group 3 had more % BG in target range compared to group 1 and 2 (69% group 3 vs 22% group 2 and 24% group 1, $P < 0.01$) • Both groups 2 and 3 had lower rates of hypoglycemia than group 1 (2.1% group 2 and 1.4% group 3 vs 5.4% group 1, $P = 0.05$) |

| | | | | | | | |
|----------------|------|------------------------------------|----|--|--|------------|---|
| Dickerson [17] | 2013 | Retrospective cohort study | 66 | <ul style="list-style-type: none"> Critically ill +/- DM USA | <ul style="list-style-type: none"> 1. IV RI continuous therapy -> transitioned to SC NPH + IV RI correction 2. IV RI correction -> added SC NPH | Continuous | <ul style="list-style-type: none"> Group 1 had lower mean glucose levels (125 vs 133 mg/dL, $P < 0.01$) Group 1 had greater time in range (18 vs. 15 h per day, $P < 0.05$) Hypoglycemia did not differ. |
| Murphy [18] | 2014 | Retrospective and prospective arms | 46 | <ul style="list-style-type: none"> All inpatients DM United Kingdom | <ul style="list-style-type: none"> 1. Retrospective SC 70/30 insulin regimen while on tube feeds 20 h/day 2. Prospective SC glargine + SC short acting insulin while on three times daily bolus feeds 3. Prospective SC glargine while on continuous tube feeds | Various | <ul style="list-style-type: none"> No difference in mean BG levels between groups Group 2 had less hypoglycemia during feeds (4% group 1, 0% group 2, 7% group 3, $P = 0.004$) |
| Hijaze [19] | 2017 | Retrospective cohort study | 53 | <ul style="list-style-type: none"> Non-critically ill DM Israel | <ul style="list-style-type: none"> 1. Glargin or Detemir + Aspart, Lispro or Glulisine nutritional and correction 2. NPH insulin three times daily | Continuous | <ul style="list-style-type: none"> No difference in mean BG Hypoglycemia did not differ |

EN enteral nutrition; DM diabetes mellitus; BG blood glucose; SC subcutaneous; N/S not specified; RI regular insulin

per dose compared to patients that received glargine 0.2 units/kg with lispro, aspart, or glulisine short-acting insulin nutritional (0.1 unit/kg) and correction coverage [19]. They found no significant differences in mean glucose levels or rates of hypoglycemia (<70 mg/dL) between these two groups. In another study, Hsia et al. analyzed 22 patients who received either glargine with lispro nutritional and correction coverage, 70/30 (premixed 70% NPH, 30% regular) insulin twice daily with lispro correction or 70/30 insulin three times daily with lispro correction [16]. The group on 70/30 three times daily had more glucose levels in the target range (140–180 mg/dL) compared to the other two groups, and both 70/30 groups had lower rates of hypoglycemia (<70 mg/dL) compared to the glargine with lispro group. The last study that looked at patients who were all on continuous EN examined transitioning from IV insulin only regimens to hybrid regimens with subcutaneous NPH in the trauma ICU [17]. They analyzed 66 patients who were either on IV regular insulin continuous therapy that were transitioned to subcutaneous NPH insulin every 12 h with IV regular insulin correction or who were on IV regular insulin correction only and had subcutaneous NPH insulin every 12 h added. The starting NPH dose was calculated as 30–50% of the total IV requirements from the prior 24 h and divided into two doses and titrated as needed throughout the study. The group transitioned from continuous IV insulin therapy to NPH with correction IV insulin had lower mean glucose levels, greater time in target range (70–149 mg/dL), and similar rates of moderate (40–59 mg/dL) and severe (<40 mg/dL) hypoglycemia to the other group.

One study examined patients on bolus EN specifically. Grainger et al. studied 52 patients on bolus EN every 4 h in the CICU who either received pre-prandial insulin (regimen was not further detailed) or glargine with lispro insulin nutritional and correction coverage [14]. They used a lispro insulin to carbohydrate ratio of 1:15 for patients with a BMI of less than 30 and a 1:10 ratio for those with a BMI of greater than or equal to 30. The glargine with lispro group had lower mean glucose levels and more glucose values in the target range (80–140 mg/dL), but more hypoglycemia (<79 mg/dL), than the pre-prandial insulin only group. Murphy et al. designed a study with a retrospective arm and two prospective arms that examined 46 patients on different insulin regimens and different tube feed schedules [18]. Group 1 was the retrospective arm of patients on a 70/30 insulin regimen (the authors used UK nomenclature of 30/70 to designate regular/NPH) and on enteral feeds 20 h per day. Group 2 was a prospective arm on glargine insulin and pre-prandial short acting insulin three times daily and on three daily bolus feeds. Group 3 was a prospective arm on glargine insulin only and on continuous EN. There was no difference in glucose control between groups, but there was a reduction in the rate of hypoglycemia, defined as <4 mmol/L (<72 mg/dL), that occurred during feeds in group 2 compared to groups 1 and 3.

Clinical Decision Support/Calculators

As presented in the previous sections, patients receiving EN may receive every 4–6 h short- or rapid-acting nutritional insulin and/or correction insulin (with or without basal insulin), or intermediate-acting insulin such as every 6–12 h

NPH-based therapies. With these standard approaches, achieving appropriate glucose control may be delayed as timely adjustments in insulin doses are rarely made to titrate to the initial needs of the individual patient. Even if the initial dosing happened to achieve control, the rate of EN is often slowly increased, and changes in insulin dosing will need to be made. One promising approach to improve glycemic control is integration of real-time glucose data with electronic prescribing to create insulin-treatment algorithms that titrate insulin doses based on glucose trends. Historically, intravenous (IV) insulin algorithms are routinely used in the ICU or perioperative setting, where nurses adjust insulin infusion rates every 1–2 h based on glucose levels. While this method may be useful for the short term in an ICU, it is labor-intensive. Even if automated IV insulin algorithms are used, they are only used for the short term, and then patients are transitioned to one of the insulin regimens described above. To achieve the individualization of the IV insulin approach with subcutaneous insulin, paper-based algorithms were developed that allowed insulin doses to be adjusted to the needs of an individual patient [21, 22]. Each of these subcutaneous insulin algorithms, when used in the ICU or perioperative settings, achieved similar glycemic control compared to IV insulin infusions.

With the introduction of electronic health records (EHRs), these subcutaneous insulin algorithms have been programmed to assist in automatically adjusting subcutaneous rapid-acting insulin to the needs of the individual patient and to adjust over time to any changes in the rate or type of enteral feedings. The patient's nurse enters in the current glucose level in a calculator in the EHR, and based on the previous glucoses and insulin doses, a new insulin dose is shown. In the initial pilot study of this automated algorithm, patients were on this algorithm for 16–404 h, the every 4-h insulin doses ranged from 0 to 21 units (average 4.5 units), and the average glucose at 72 h was 156 mg/dL [23]. After the first year of full implementation, the automated algorithm, without need for physicians to make any daily adjustments, led to results similar to the initial pilot and when compared to standard treatment resulted in significant decreases in average glucose values and reduction in hypoglycemia [24].

Practical Strategies

As we have reviewed here, there is insufficient evidence to recommend any specific strategy for the management of diabetes and hyperglycemia in patients receiving enteral nutrition. There are therefore several reasonable approaches that we have outlined in Fig. 27.1, with further details on example insulin regimens for continuous EN detailed in Table 27.3. We recommend starting by assessing whether the patient has type 1 diabetes or is status post (s/p) total pancreatectomy. The second step is to determine the EN schedule: continuous, cyclic, or bolus. The duration of cyclic tube feeding must be determined, whereas bolus tube feeding information must include the frequency (e.g., Q4 hr) or the number of boluses being administered per day. If the patient has type 1 diabetes or is s/p total pancreatectomy, then basal insulin must be continued in addition to the regimen being used for

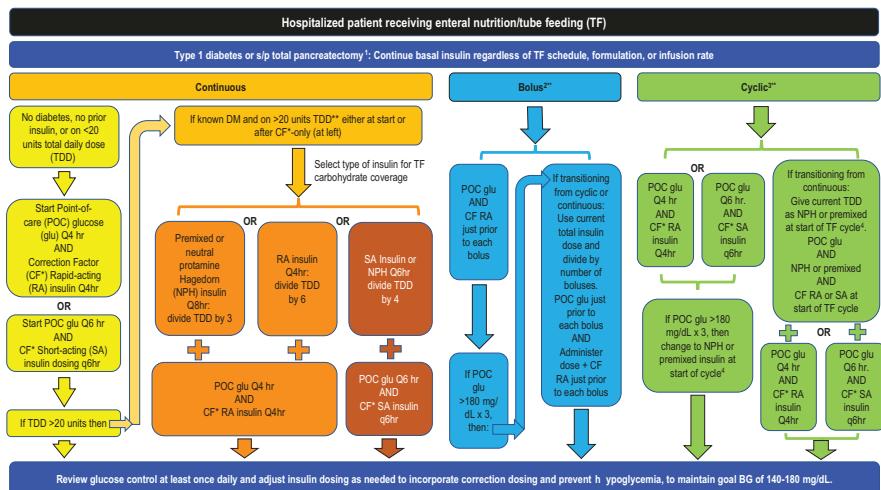


Fig. 27.1 Management of hyperglycemia and diabetes in the hospitalized patient receiving enteral nutrition/tube feeding (TF). Footnotes: ¹Basal insulin must be continued with any type of TF since any interruption of insulin will place patient at risk for diabetic ketoacidosis (DKA). ²Defined as TF administered three to five times per day at scheduled intervals, infused quickly (i.e., over less than 1 h). ³If also eating, order appropriate insulin for meal coverage. ⁴For example: Take total dose of insulin given during that time and instead give as premixed insulin or NPH at start of TF cycle. Some patients may need an additional dose of premixed insulin or NPH mid-way through the cycle if duration of TF is longer than 8 h. * CF (correction factor) insulin example scales: **Sensitive**—for BMI <25 kg/m², type 1 diabetes, renal or hepatic impairment, elderly or frail: 1 unit of rapid-acting or short-acting insulin for every 50 mg/dL that glucose is above 130 mg/dL; **Resistant**—“medium” scale, for most with type 2 diabetes and/or BMI ≥ 25 kg/m²: 2 units of rapid-acting or short-acting insulin for every 50 mg/dL that glucose is above 130 mg/dL; **Very Resistant**—not for initial use unless patient is on 100 or more units of insulin total per day in hospital; start with Resistant scale and transition to this if resistant scale insufficient for glycemic control: 3 units rapid-acting or short-acting insulin for every 50 mg/dL that glucose is above 130 mg/dL. ** In patients with known DM, may consider starting scheduled carbohydrate coverage immediately using a carbohydrate ratio of 1:10–1:15 (see text). Basal Insulin: for example, glargine, detemir, or degludec. Premixed insulin: for example, Novolin 70/30, Humulin 70/30, Novolog 70/30 or Humalog 75/25. Abbreviations: CF correction factor insulin; NPH neutral protamine Hagedorn insulin; POC point-of-care; RA rapid-acting insulin (e.g., aspart, lispro, glulisine); SA short-acting insulin (regular insulin)

management of EN; the basal insulin must be continued during EN interruptions. In some patients with type 2 diabetes (T2D) including those requiring a higher total daily dose of insulin, or who were on basal-bolus insulin prior to admission, starting or continuing basal insulin in addition to the regimens that follow should be considered.

If the patient does not have a diagnosis of diabetes or has T2D and has been on approximately 20 or fewer units of insulin total per day before EN initiation, then scheduled nutritional insulin to address carbohydrate content of EN may not be required, and initial management with point of care (POC) glucose checks and rapid-acting insulin according to a correction factor (RA CF) every 4 h would be a

Table 27.3 Insulin example strategies for continuous tube feeding (TF)

| Regimen | Purpose | | | POC glucose | Insulin dosing | Comments |
|--------------------------------------|---------------------------|--------------|---------------------|-------------|--------------------|--|
| | Basal | Nutr | Corr | | | |
| IV insulin | IV | IV | IV | Q1–2 h | Adjustments Q1–2 h | <ul style="list-style-type: none"> • Quick offset for TF interruption • Not adequate for PO intake • Q1 h unless stable infusion rate \times 4 h, then Q2 h |
| Basal-bolus | Glargine | Lispro | Lispro ^b | Q4 h | Q4 h | <ul style="list-style-type: none"> • High hypoglycemia risk due to unplanned TF interruptions unless glargine is NOT being used to address nutritional needs and is <20–30% total daily dose |
| 70/30 or NPH Q8 h + Lispro | +/- Glargine ^a | 70/30 or NPH | Lispro ^b | Q4 h | Q8 h | |
| Regular insulin or NPH Q6 h + Lispro | +/- Glargine ^a | Reg or NPH | Lispro ^b | Q6 h | Q6 h | |
| IV + 70/30 or NPH Q8 h | IV | 70/30 or NPH | IV | Q1–2 h | Q1–2 h | <ul style="list-style-type: none"> • May be used when transitioning off IV • Q1 h unless stable gtt rate \times 4 h then Q2 h |

Abbreviations: *Corr* correctional insulin; *IV* intravenous; *NPH* neutral protamine Hagedorn; *Nutr* nutritional insulin; *PO* per os; *POC* point-of-care; *Gtt drip*

^a Glargine for all T1D or total pancreatectomy patients and some T2D

^b If nutritional insulin is adjusted to TF needs, less correction dosing is needed

reasonable approach. If the patient demonstrates that they need more than 20 units of correction insulin after EN initiation or they have T2D and were on >20 units of insulin daily prior to EN, then nutritional coverage should be initiated. Patients on continuous EN may have nutritional needs addressed using either: (1) 70/30 or NPH every 8 h (total daily correction dose divided by 3 for each dose) plus RA CF every 4 h, (2) rapid acting insulin every 4 h (total daily correction dose divided by 6) plus RA CF every 4 h, (3) regular insulin every 6 h (total daily correction dose divided by 4) plus RA CF every 4 h, or (4) NPH every 6 h (total daily correction dose divided by 4) plus RA CF every 4 h. Some institutions will administer RA CF every 6 h if using NPH or regular insulin every 6 h, to align workflow.

Patients on bolus EN may have nutritional needs addressed using rapid-acting insulin prior to each bolus feed. The starting dose can be calculated by dividing the total daily correction dose by the number of bolus feeds per day, plus RA CF before every bolus feed, approximately every 4 h (Fig. 27.1). An alternative would be to

calculate the RA dose for each bolus using the carbohydrate content of the bolus and an estimated carbohydrate ratio.

If the EN is cyclic, then the patient can receive a dose of either 70/30 or NPH insulin at the start of the cycle (Fig. 27.1). Depending on the duration of feeds, another dose mid-way through the cycle may be needed to prevent hyperglycemia at the end of the EN cycle. Starting doses of insulin to address nutritional needs can be calculated using an insulin to carbohydrate ratio (by calculating the grams of carbohydrates delivered in the EN formula) rather than using the TDD from days on correction-only insulin or home doses, especially for bolus and cyclic tube feedings. Initial carbohydrate ratios ranging from 1 unit of insulin for every 10 gm of carbohydrates to 1 unit for every 15 gm of carbs are often recommended [9].

In the case of EN interruptions, a 5% dextrose (D5) or 10% dextrose (D10) infusion should be started to avoid hypoglycemia [25]. A D5 infusion is often started at a rate equivalent to the rate that EN was running, but the D5 or D10 infusion rate should be adjusted to avoid hypoglycemia. The dextrose infusion should be continued for the duration of the longest-acting insulin that the patient received most recently for nutritional coverage. Please refer to Chap. 3 for more information on hypoglycemia.

Selected commonly used tube feeding formulas with calculated carbohydrate content per milliliter are outlined in Tables 27.4, listed alphabetically and ranked by carbohydrate content (Table 27.5).

Table 27.4 Carbohydrate content of selected tube feeding (TF) formulations^a

| Formulation | Carbohydrate content (grams of carbohydrate per mL of TF) | Formulation | Carbohydrate content (grams of carbohydrate per mL of TF) |
|---------------------|---|---------------------|---|
| Ensure | 0.138 | Nutren | 0.128 |
| Glucerna 1.2 | 0.114 | Nutren 1.5 | 0.176 |
| Glucerna 1.5 | 0.133 | Nutren 2.0 | 0.216 |
| Impact | 0.148 | Osmolite 1.5 | 0.203 |
| Impact peptide | 0.140 | Peptamen 1.0 | 0.126 |
| Isosource | 0.140 | Peptamen AF 1.2 | 0.112 |
| Isosource 1.5 | 0.176 | Peptamen 1.5 | 0.188 |
| Isosource HN | 0.156 | Peptamen intense | 0.076 |
| Jevity | 0.140 | Replete | 0.112 |
| Jevity 1.5 | 0.216 | Suplena | 0.194 |
| Nepro | 0.160 | Vivonex RTF | 0.176 |
| Novasource | 0.181 | Twocal HN | 0.094 |
| Novasource renal | 0.183 | | |

^a Values were calculated using information obtained from manufacturers' websites and were correct at the time of publication

Table 27.5 Above tube feeding (TF) formulations ranked by carbohydrate content^a

| Formulation | Carbohydrate content (grams of carbohydrate per mL of TF) | Formulation | Carbohydrate content (grams of carbohydrate per mL of TF) |
|------------------|---|------------------|---|
| Peptamen intense | 0.076 | Isosource HN | 0.156 |
| Twocal HN | 0.094 | Nepro | 0.160 |
| Peptamen AF 1.2 | 0.112 | Isosource 1.5 | 0.176 |
| Replete | 0.112 | Nutren 1.5 | 0.176 |
| Glucerna 1.2 | 0.114 | Vivonex RTF | 0.176 |
| Peptamen 1.0 | 0.126 | Novasource | 0.181 |
| Nutren | 0.128 | Peptamen 1.5 | 0.188 |
| Glucerna 1.5 | 0.133 | Novasource renal | 0.183 |
| Ensure | 0.138 | Suplena | 0.194 |
| Impact peptide | 0.140 | Osmolite 1.5 | 0.203 |
| Isosource | 0.140 | Jevity 1.5 | 0.216 |
| Jevity | 0.140 | Nutren 2.0 | 0.216 |
| Impact | 0.148 | | |

^a Values were calculated using information obtained from manufacturers' websites and were correct at the time of publication

Future Horizons

In addition to the automated subcutaneous insulin algorithms being developed and implemented that we discussed in the "Clinical Decision Support/Calculators" section, closed-loop insulin pump systems may be a management option on the horizon for this population. Boughton et al. performed a two center RCT in patients on EN and/or parenteral nutrition who had inpatient hyperglycemia [26]. Forty-three patients were randomized to either receive closed-loop insulin delivery through a study pump with faster-acting insulin aspart (FiAsp) that received data from a continuous glucose monitor (CGM) or to a control group. The control group received conventional subcutaneous insulin therapy in accordance with the institution's local practice and were also placed on a CGM. The proportion of time that the sensor glucose values were in the target range, 5.6–10.0 mmol/L (100–180 mg/dL), was far higher in the closed-loop system group at 68.4% compared to the control group, 36.4%, $p < 0.0001$. Rates of hypoglycemia, glucose <3.9 mmol/L (70 mg/dL), were low and did not differ between the two groups (0.5% of the time for both). Furthermore, CGMs themselves likely have a key role in inpatient glucose management, and this is an active area of investigation. There have yet to be studies using CGMs in inpatients on EN specifically, but their utility was demonstrated in a case report of a man on parenteral nutrition-induced hyperglycemia complicated by the insulin resistance of a severe COVID 19 infection [27]. CGM helped the team titrate his insulin aggressively (up to a TDD as high as 128 units) and safely without any episodes of hypoglycemia.

Conclusion

The prevalence of EN-associated hyperglycemia in hospitalized patients is considerable. Patients with EN-associated hyperglycemia receiving insulin therapy are at risk for hypoglycemia due to several EN-specific factors. There must be clear communication among the care team regarding changes in EN delivery that can impact glycemic control and/or increase risk for hypoglycemia. The optimal approach would be effective for control of EN-associated hyperglycemia, minimize the risk for hypoglycemia, and be straightforward enough to minimize errors. There is a paucity of high-quality evidence for optimal management strategies. This chapter summarizes the available literature and outlines suggested management strategies based on the experience and opinions of the authors. More evidence is needed regarding optimal insulin regimens, initial dosing and subsequent titration of insulin, and use of non-insulin antihyperglycemic agents. In addition, evidence for the utility of continuous glucose monitoring systems in this setting is needed, along with data to support use of commercially available automated insulin delivery systems for EN-associated hyperglycemia. This is clearly an area that requires further study to better inform our care of hospitalized patients.

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Chapter 28

Diabetes and Parenteral Nutrition



Michael A. Via

Introduction

The modern clinical practice of parenteral nutrition (PN) administration that has been developed over the past six decades allows for the direct infusion of nutritional elements into the vascular space. In appropriate patients, this can provide adequate macronutrients (amino acids, dextrose, lipids), micronutrients (electrolytes, vitamins, minerals), and water without the need for oral dietary consumption [1]. PN is often reserved for specific clinical scenarios that mainly include patients with a nonfunctional gastrointestinal (GI) tract [1]. When indicated, PN can serve to sustain a patient as the sole source of nutrition for prolonged periods as dictated by the clinical needs of the patient [1, 2]. Cases of PN use for years have been reported [1, 2].

PN is commonly denoted as total parenteral nutrition (TPN) in the setting of complete or approximately complete intravascular administration of nutritional requirements. Due to the high osmotic load of TPN formulas, the safe delivery of TPN must be given through a central venous catheter [3]. Infusion protocols of TPN allow for flexibility in that they may be given continuously over 24 h or for a shorter duration, such as over 10–18 h, when clinically appropriate. In contrast, the term partial parenteral nutrition (PPN) refers to the administration of PN formulas that contain only a fraction of a patient's daily nutritional needs [3]. The single advantage of PPN formulas is that they may be infused through peripheral intravenous (IV) access. However, several glaring disadvantages of PPN exist. These include insufficient nutritional content of PPN leading to the questionable efficacy of PPN. Additionally, there is a need for high fluid volume in PPN to maintain the

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lower osmolyte pressures that are tolerated in peripheral veins. Despite this, there may be a sensation of burning or other discomfort to the patient during infusion as well as risk for thrombophlebitis. IV infusion sites are changed every 2–3 days [3, 4]. For these reasons, use of PPN is minimized and discouraged in most practices [3, 4]. The principles outlined in this chapter mainly refer to patients receiving TPN, though similar considerations may be taken in rare instances of PPN use.

The indications for PN among patients with diabetes mellitus, including both in type 1 diabetes (T1D) and type 2 diabetes (T2D), are similar to indications for patients without diabetes [1, 5]. However, in patients with T1D, T2D, or prediabetes, the administration of PN use must include considerations to minimize metabolic risks such as effects on glycemia, serum triglycerides, liver disease, and care to minimize the risk of infection [6].

Indications for PN

The need for nutrition is ubiquitous. Perhaps, as a consequence, guidelines and recommendations for the administration of PN are based on both clinical evidence and expert consensus [1, 5]. The earliest supportive evidence was observed in a randomized trial of PN administration preoperatively in planned surgical patients that showed benefit among the subgroup of patients with severe malnutrition [7]. Similar beneficial findings were noted among a group of hospitalized patients with severe malnutrition who were given PN [8].

Outside of cases of severe malnutrition, PN is also indicated among patients with insufficient oral dietary intake and nonfunctional GI tract for 7–10 days regardless of baseline nutritional status [1, 5]. This includes patients with disrupted GI function, such as following abdominal surgery, enterocutaneous or other fistula development, bowel obstructions that require prolonged GI rest, injury to the thoracic duct with resultant chylothorax, inflammatory disease of the GI tract, or GI tract ischemia [9, 10]. Malabsorption of nutrients secondary to diseases of the GI tract represents another indication for PN such as in cases of Crohn's disease, or in short bowel syndrome due to previous surgery [10]. The need for PN may arise in patients following malabsorptive bariatric surgery [Roux-en-Y gastric bypass, biliopancreatic diversion (BPD) or BPD with duodenal switch] [6]. Patients with severe malnutrition resulting from disordered eating, including anorexia nervosa, which present emergently with signs of anasarca, cardiac dysfunction, renal insufficiency, or systemic shock, may also benefit from a temporary course of PN [11].

In critically ill patients who are not malnourished, a number of randomized clinical trials have been conducted that investigate use of PN within the first 7 days of intensive care unit admission. In this group of trials, no clear benefits for PN were demonstrated, although several improvements were inconsistently observed [12]. The most common benefit with early PN administration is a reduction in observed rates of hypoglycemia [13]. Based on these findings, the practice of early PN administration in patients with critical illness is not recommended [14]. However,

critically ill patients with insufficient oral dietary intake extending beyond 7 days may be considered for PN [14, 15].

PN use is controversial, and it is generally discouraged among patients with chronic disease who may be malnourished [1, 5]. This includes in patients with advanced cancer or cardiac cachexia for whom no clear benefit of PN administration is observed [1, 5].

Complications

When indicated, use of PN must be weighed against potential risks. Line infections, liver disease including both cholestasis and hepatosteatosis, hypertriglyceridemia, and hyperglycemia are among the most common complications associated with PN administration, with risks for each exacerbated in patients with diabetes mellitus. Table 28.1 provides a summary of PN-associated risks and suggested strategies for risk reduction.

Table 28.1 Summary of parenteral nutrition (PN)-associated risks and suggested strategies for risk reduction

| PN-associated risk | Prevalence | Clinical strategies |
|---|--------------------------------------|--|
| Line infection | 10–14% [18] | <ul style="list-style-type: none"> – Sterile line insertion [19] – Careful hygiene with line manipulation [19] – Targeted glycemic control (serum glucose 110–180 mg/dL) [9] |
| Liver disease (cholestasis and hepatosteatosis) | Up to 50–60% over the long term [22] | <ul style="list-style-type: none"> – Reduced dextrose content (3 mg/kg/min or less, ideally 1.8 mg/kg/min or less) [22] – Use of fish oil-based lipid formulation [29] – Adequate vitamin E provision [28] |
| Hypertriglyceridemia | 6–20% [37] | <ul style="list-style-type: none"> – Reduced dextrose content (3 mg/kg/min or less) [38] – Use of fish oil-based lipid formulation [9] – Reduce lipid content titrated to response [40] – Cessation of PN infusion if severe hypertriglyceridemia [9] |
| Hyperglycemia | 17–51% [41] | <ul style="list-style-type: none"> – Reduced dextrose content (1.3–3 mg/kg/min) [48, 51] – Regular insulin added to the PN formula starting at 1 unit for every 10–20 g carbohydrates or based on home insulin dosing [49] – Alternate modes for insulin delivery – Regular or rapid insulin subcutaneous every 3–6 h [6] – Long-acting insulin once daily, with a need for dextrose if PN infusion is disrupted [6] – Intravenous insulin protocol [61] – Subcutaneous insulin pump [64] – Closed-loop continuous glucose monitor–subcutaneous insulin pump system [65] – Adequate micronutrient provision (chromium, thiamine, biotin) [54, 56, 57] |

Line Infection

Central catheter or line infections are observed in approximately 10–14% of patients receiving PN [16–18]. In one series, the infectious agent was identified as either bacterial as gram-negative rods (37%) or gram-positive cocci (38%); or as fungal (25%) [17]. This wide range of potential causative microorganisms necessitates broad antibiotic therapy that may be modified after identification of the specific infectious etiology and antimicrobial agent susceptibilities [10].

The risk of PN-associated line infection is slightly increased among patients with diabetes mellitus. In a series of patients in the community who were receiving PN, the presence of diabetes of any type demonstrated a minor increase in risk for line infection (OR 1.11; 95% CI 1.02–1.15) [19]. It is unknown whether targeted glycemic control mitigates this specific risk. However, since maintaining blood glucose levels between 110 mg/dL (6.1 mmol/L) and 180 mg/dL (10 mmol/L) demonstrates reduced overall rates of infection, this range is recommended for patients receiving PN [9, 10, 20]. Among patients with critical illness receiving PN, the recommended target glucose range is between 140 mg/dL (7.8 mmol/L) and 180 mg/dL (10 mmol/L) [9].

Hygienic practices that minimize infection risk are also recommended for all patients receiving PN. These include sterile technique for line insertion, sterile technique for PN catheter connection manipulation, and strict hand hygiene [19, 21].

Liver Disease

Liver disease is associated with intestinal failure and PN administration. The pathophysiology of PN-associated liver disease includes both cholestasis and hepatosteatosis. Severity of cholestasis may range from mild increases in serum alkaline phosphatase and bilirubin levels to more extreme hyperbilirubinemia and frank jaundice. Approximately 50–60% of patients receiving PN demonstrate signs of cholestasis, with rates that increase over the longer term [22]. This is attributed to a loss of endocrine and paracrine signaling from prolonged intestinal disuse as well as metabolic effects of PN components [22]. Similarly to cholestasis, long-term studies show 50–60% of patients receiving PN develop hepatosteatosis, with both hepatic processes commonly occurring simultaneously [22]. Short-term development of PN-associated hepatosteatosis over a period of weeks has also been reported [23].

A number of factors are believed to contribute to the development of hepatosteatosis in patients receiving PN. Intravenous feeding bypasses the incretin hormone system that results in omission of release of glucagon-like peptide (GLP)-1, GLP-2, and fibroblast growth factor-19 by cells of the intestine [24]. This absence of incretin activity impairs hepatic lipid metabolism and contributes to hepatic adipose accumulation [24, 25]. PN also activates the hepatic AKT2 tyrosine kinase pathway

and inhibits hepatic adenosine monophosphate-activated protein kinase pathway within hepatocytes, both contributing to hepatosteatosis [26, 27]. Additionally, epigenetic changes in peroxisome proliferator-activated receptor (PPAR)- γ and ACC2 genes within hepatocytes are induced by PN feeding, which further contribute to the development of hepatosteatosis [28].

Outside of these general effects of PN liver and intestinal physiology, aspects of several specific PN formula components may play a role in liver disease. Among the most prominent is the use of soy oil-based lipid formulations [29]. Soy oil contains high amounts of ω -6 long-chain essential fatty acids as well as hepatotoxic phytosterols. Both of these factors induce hepatosteatosis through local toxicities as well as through enhancement of systemic inflammation [29]. Moreover, signaling from glycoprotein receptor-120 bound to ω -3 fatty acids has been shown to reverse hepatosteatosis among patients with alcohol-induced hepatic injury [30]. A predominance of ω -6 fatty acids provided by soy derived lipids would impair this process [30].

In contrast, the use of a PN lipid formulation derived from fish oil, which is high in ω -3 fatty acids, can reduce both hepatosteatosis and cholestasis associated with PN use [29, 31]. In one study, 12 of 15 patients with PN-associated liver disease demonstrated normalization of serum bilirubin 1 month after changing to a fish oil-based lipid source. Additionally, improvement in serum liver enzyme levels and an approximate 30% reduction in histologic score of hepatosteatosis and fibrosis was observed over 1 month of follow-up [31].

Dextrose content is another factor for development of hepatosteatosis. In patients receiving PN, the risk of liver fat deposition is proportional to the rate of dextrose infusion [23]. A high dextrose content at levels greater than 5 mg dextrose per kg body weight per minute (mg dextrose/kg/min) place the patient at greatest risk [23]. Lower rates of dextrose infusion, such as 1.8 mg dextrose/kg/min, confer only modest risk, and mid-range rates of 3–4 mg dextrose/kg/min have moderate risk over the long term [23, 32]. Minimizing dextrose infusion can prevent and treat PN-associated hepatosteatosis.

Vitamin E deficiency is also common among patients receiving PN and is either absent or provided at low levels in most PN formulas [28]. As a lipid-soluble antioxidant, vitamin E can reverse hepatosteatosis, and deficiency of vitamin E may contribute to PN-associated liver toxicity [33]. PN formulas supplemented with α -tocopherol demonstrate histologic improvement in animal models of PN-associated hepatosteatosis [28]. In addition, PPAR γ and ACC2 gene expression normalized with α -tocopherol supplementation, which would be expected to prevent hepatosteatosis [28].

The approach to a patient who develops PN-associated liver disease should employ one or more of these strategies: (1) change to a fish oil-based lipid formulation, (2) reduce dextrose infusion rate ideally to 1.8 mg dextrose/kg/min, and (3) provide supplemental vitamin E [10, 15, 34]. A combination of these strategies may be tailored to severity of disease. In the most severe cases, or in patients who fail to respond, cessation of PN infusion may be required.

Outside of PN use, hepatosteatosis is commonly present among patients with obesity (prevalence 50–80%) and among patients with T2D (prevalence 70–90%)

[35, 36]. In the general US population, a 24% prevalence of hepatosteatosis is reported [36]. It is presently unknown what role pre-existing hepatosteatosis may play in the development of PN-associated liver disease. When PN is indicated in a patient with either known hepatosteatosis or in a patient at high risk for hepatosteatosis (e.g., with obesity or with T2D), a prudent approach may include similar precautions to minimize risk including PN initiation with reduced dextrose content, use of a fish oil derived lipid formulation, and consideration for vitamin E supplementation [10, 15, 34].

Hypertriglyceridemia

An increase in serum triglyceride levels follows initiation of PN infusions that contain lipids, especially among patients with malnutrition secondary to intestinal failure. In 6–20% of cases, triglyceride levels exceed 200 mg/dL [37]. Risk factors for PN-associated hypertriglyceridemia include diabetes of any type, obesity, hyperglycemia, and renal impairment, sepsis, multi-organ failure, and alcoholism [38]. In the acute setting, mild hypertriglyceridemia may be tolerated, though more severely high triglyceride levels increase risk for pancreatitis. There is no consensus for the upper limit of tolerance; published recommendations for the maximum allowable triglyceride levels during PN administration vary from as low as 400 mg/dL to as high as 1000 mg/dL [9, 38]. In general, pancreatitis is unlikely to occur when triglyceride levels are less than 1000 mg/dL [39].

Several factors affecting triglyceride levels during PN administration are the type of lipid formulation, the amount of lipid content, and the amount of dextrose content [38]. Fish oil-based lipid formulations demonstrate a modest reduction in serum triglycerides [9]. Reduction in total lipid content of the PN formula by 10–30% or greater can also reduce serum triglyceride levels in proportion to the degree of lipid reduction [40]. Additionally, dextrose infusion rates greater than 3 mg/kg/min are associated with increased rates of hypertriglyceridemia [38].

Among patients with T1D or T2D, especially those with pre-existing hypertriglyceridemia, strategies to reduce risk of PN associated hypertriglyceridemia should be implemented [9]. These may include limiting the dextrose infusion rate to 3 mg/kg/min or less, or changing to a fish oil-based lipid formulation [9]. If severe hypertriglyceridemia develops, temporarily withholding lipids from the PN formula may be necessary to reduce risk of consequent pancreatitis [9].

Hyperglycemia

Hyperglycemia is a common adverse effect in PN administration. The observed prevalence varies somewhat: studies report hyperglycemia developing in 17–51% of patients receiving PN [41–43]. Observed risks of mortality are reported as

increased among hospitalized patients who develop hyperglycemia while receiving PN [44]. Increased risk of infection and cardiac complications are also observed in this group [44]. Risk factors for hyperglycemia include history of T2D (OR 11), critical illness (OR 3.3), or concurrent corticosteroid therapy (OR 3.2) [45]. Adverse outcomes are observed in patients with PN-associated hyperglycemia including between a 2- to 11-fold increased rate of mortality, as well as increased risk of line infections (OR 3–4), cardiac complications (OR 1.7–5), and development of renal insufficiency [44, 46–48]. The greatest risk of complication is noted among patients who develop PN-associated hyperglycemia but have no history of diabetes [44].

To mitigate risk, glycemic control is recommended for patients receiving PN with a target range between 110 mg/dL (6.1 mmol/L) and 180 mg/dL (10 mmol/L) [1, 5, 10]. These recommended goals are extrapolated from randomized studies of glycemic targets in hospitalized patients, of which most were not receiving PN.

A combination of several strategies may be employed to prevent or treat hyperglycemia in a patient who is prescribed PN. Prior to initiation of PN, identification of high risk patients is essential. These include patients with a history of T2D, patients with baseline hyperglycemia (such as hyperglycemia associated with stress of acute illness), or patients with critical illness. Special considerations should be taken regarding insulin therapy for patients with T1D, who are also at risk for hyperglycemia.

Hyperglycemia Prevention and Treatment Strategies

Strategies to diminish hyperglycemia in patients receiving PN are not mutually exclusive. In appropriate clinical settings, this may include direct addition of insulin to the PN formula, adjustment of dextrose content, and addressing possible micro-nutrient deficiencies that may cause insulin resistance.

Add Insulin Directly to PN Formula

Regular human insulin is stable within PN formulations and may be added to treat or prevent hyperglycemia. A reasonable starting dose is about 1 unit of insulin for every 10–20 g of dextrose in the PN formula (equivalent to 0.05–0.1 units insulin per g dextrose). This starting point should be modified based on previous insulin requirements and adjusted based on response [49].

Advantages of this approach include continuous insulin activity given simultaneously with intravenous dextrose. This consumes less nursing time and leads to automatic cessation of insulin if the PN infusion is disrupted. Disadvantages include the need to adjust dosages of other insulin that may be concomitantly administered, the potential for insulin to bind to the PN formula bag or tubing, and no ability to independently lower the insulin dose without lowering the rate of PN infusion if

hypoglycemia develops during the typical 12- to 24-h PN infusion times. In the case of hypoglycemia from excessive PN insulin, a separate dextrose infusion should be started or cessation of PN should be considered until a new formula with less insulin can be administered [6]. While PN cessation may be necessary to address hypoglycemia, this practice reduces nutritional intake for patients, exacerbating malnutrition that is already present.

A single head-to-head trial has been published that compares a protocol of regular insulin added to the PN formula with a standard subcutaneous insulin regimen given to hospitalized patients receiving PN [50]. Similar degrees of glycemic control are noted in both groups, validating the practice of direct insulin addition to PN.

Use of Insulin outside PN

The advantages of insulin added directly to PN make this route preferred in most circumstances. However, some clinicians may select a subcutaneous insulin regimen due to practice familiarity. Several precautions should be taken in patients receiving PN that are prescribed additional subcutaneous insulin. (1) Both the insulin and the PN should be ordered by the same prescriber or by a highly communicative team to minimize asynchronous changes to the PN carbohydrate content and insulin dose. (2) The diabetes provider should review whether the PN infusion is continuous over 24 h or cycled for a shorter duration. (3) Insulin dosing should be similar to in-formula insulin: starting with 1 unit for every 10–20 g carbohydrates, or with the use of home insulin dose to estimate an insulin-to-carbohydrate ratio. (4) The type of insulin should be selected with potential for PN disruption in mind. If the total daily dose is divided into multiple small doses of rapid insulin or regular insulin given every 3–6 h, these should be discontinued if the PN infusion is stopped. If a single dose of long-acting insulin is given daily, intravenous dextrose must be infused if PN is disrupted to minimize risk of hypoglycemia from continued insulin activity. (5) In addition, a corrective scale for subcutaneous rapid insulin given every 6 h may serve to address hyperglycemia that develops despite standing insulin. In each of these points, strong communication between the diabetes provider and the nutrition support team is essential.

Minimize d-Glucose (Dextrose) Content of the PN Formula

The dextrose content of PN may be adjusted to meet calorie needs of each individual patient. At levels of more than 3 mg dextrose/kg/min, increased risk of hyperglycemia is noted [48]. Limiting dextrose content of the PN formula to lower levels reduces hyperglycemia rates [6]. In one study, a decreased infusion rate of dextrose that was 1.3 mg dextrose/kg/min was shown to reduce mortality in critically ill patients receiving PN [51]. At this suggested rate of dextrose infusion, the daily

dextrose targets may fall between 150 and 200 g per 24 h [6, 44]. If hyperglycemia develops or persists, dextrose content may be lowered further, as no minimum daily requirement exists for this macronutrient. Moreover, a reduction in calorie content in acute or critical illness does not appear to affect measurable outcomes including mortality, length of hospitalization, or length of time spent in intensive care [52]. As with insulin dosing, any changes in carbohydrate PN content must be readily communicated to ensure synchronous adjustment of both insulin and carbohydrates.

A second strategy is to initiate the PN formula at a fraction of the intended macronutrient content and advance as tolerated over the course of 2–3 days. A common practice is to prescribe 25–50% of calories on the first day of PN infusion, advance to 50–75% on the second day, and achieve 100% of prescribed calories by the third day [13]. This allows for detection of high-normal glycemic levels or possibly mild hyperglycemia that may develop. Formula adjustment can be implemented (e.g., reduced PN dextrose and/or increased insulin content) to prevent more severe hyperglycemia from developing.

A third approach is to aggressively initiate enteral nutrition when possible. Patients receiving at least 60% of calories either by mouth or through enteral feeding tubes may be weaned from PN, which can diminish hyperglycemia [44]. In this case, subcutaneous insulin may be required.

Micronutrient Supplementation

Patients who require PN may be malnourished at baseline, which can include micronutrient deficiency. General multivitamins and trace elements mixtures are included in PN formulas. In addition, ensuring adequate levels of micronutrients specific to cellular glucose metabolism or micronutrients required in the insulin signal pathway can help to minimize hyperglycemia, especially in deficiency states.

Chromium, a micronutrient with a daily requirement of 25–35 µg, acts as a cofactor to the peptide chromodulin that enhances phosphorylation of the insulin receptor during activation [53]. Through this mechanism, chromium is required for insulin activity. Deficiency of chromium leads to severe insulin resistance characterized by hyperglycemia, hypertriglyceridemia, and painful neuropathy that resolve with chromium supplementation [53]. The addition of chromium to the infused PN formula at a dose of 20–80 µg daily can improve hyperglycemia, especially in patients at risk for deficiency [53, 54].

Thiamine is an important biochemical cofactor in dehydrogenase/decarboxylation reactions. These include both the conversion of pyruvate to acetyl-CoA at the end of glycolysis and the reduction of α -ketoglutarate to succinyl-CoA in the Krebs cycle [55]. Both of these thiamine-dependent reactions are critical in glucose metabolism. Hyperglycemia manifests as a late finding in thiamine deficiency, reported to occur after 3 weeks of a deficient state [55]. Adequate thiamine intake of 25–50 mg administered within PN can prevent development of deficiency [55].

Doses of thiamine up to 500 mg daily may be given when frank deficiency is suspected [56].

Biotin is another important cofactor that mainly functions in fatty acid metabolism [57]. Deficiency of biotin impairs this process and indirectly reduces expression of genes important in glucose homeostasis, raising glucagon activity and driving hyperglycemia [57]. Modern PN formulations generally contain adequate biotin (approximately 40 µg daily) within the standard multivitamin that is included.

Type 1 Diabetes

T1D develops in patients in which autoimmune destructive processes cause either complete or near complete loss of insulin-producing pancreatic β -cells. Other etiologies of impaired insulin secretion include chronic pancreatitis, pancreatectomy, cystic fibrosis, and hemochromatosis [58]. Significant loss of circulating insulin leads to hyperglycemia and other metabolic sequelae that can include diabetic ketoacidosis. Consequently, insulin must be administered at all times to mimic basal pancreatic insulin production. Bolused insulin is administered to prevent hyperglycemia that occurs with any nutritional ingestion. Some patients with T1D may be quite sensitive to insulin, though others may demonstrate insulin resistance and require relatively high doses of insulin.

The need for continual insulin administration as well as the importance of matching mealtime insulin with dietary intake is cause for special consideration in patients with T1D that require PN administration. The strategy, in this case, requires uninterrupted insulin infusion. Unfortunately, PN administration can be discontinued unexpectedly due to loss of central venous access, line infection, or for other less common reasons [6]. In the event of PN disruption, patients with T1D depending on insulin within the PN formula must be given subcutaneous or continuous intravenous insulin to prevent ketoacidosis [6].

Combinations of insulin doses may also help attain glycemic control and prevent ketoacidosis. In one case series, patients receiving PN were given a combination of regular insulin directly within the PN formula, as well as a minimal amount of subcutaneous insulin [59]. In this fashion, insulin activity is maintained even if the PN infusion is disrupted. When following this approach, 70–90% of the total daily insulin may be administered within the PN formula. The remaining 10–30% should be given as subcutaneous insulin, either as once daily basal insulin or as regular insulin given every 6 h [60]. This may be achieved using 0.2 units/kg to guide basal insulin dosing, with the remainder of required daily insulin given directly in the PN formula.

The daily dose of insulin may be approximated by usual “home” insulin requirements, if known. Prescribed insulin doses should be reduced by 20–30% when initiating PN to minimize hypoglycemia risk [6, 12, 60]. If a patient’s usual insulin doses are unknown, a reasonable starting dose may be 1 unit for every 20 g of carbohydrates in the PN formula, with careful monitoring and adjustment [6, 12].

Several case publications highlight other possible strategies for insulin delivery in patients with T1D receiving PN. In one method, PN was administered along with a separate intravenous insulin infusion that was adjusted for glycemic control [61–63]. This approach requires close monitoring. Subcutaneous insulin pump therapy has also been reported to achieve glycemic control in patients receiving PN [64]. More recently, some authors suggest the use of a closed-loop automated system to achieve glycemic control in hospitalized patients, including patients receiving PN therapy with hyperglycemia but without T1D [65]. Studies for closed-loop technology in patients with T1D receiving PN have not been published.

Conclusion

PN represents a distinctive life-sustaining modality to deliver nutrients in appropriate clinical scenarios. Careful administration of PN includes consideration to mitigate complications that include infection, PN-associated liver disease, hypertriglyceridemia, and hyperglycemia. Patients with diabetes of any type are at increased risk for each of these complications. Strategies such as reduction of dextrose content, use of a fish oil-based lipid formulation, appropriate micronutrient supplementation, and coordinated administration of insulin can address these risks. Through these techniques, safe administration of PN can provide adequate nutritional support.

Disclosures None.

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Part V

Diabetes Education and Transition to

Outpatient

Chapter 29

Inpatient Diabetes Education



Ann Marie Hasse, Theresa King, and Tori Calder

Introduction

According to the Centers for Disease Control in 2021, 37.3 million people (11.3% of the United States population) have diabetes mellitus (DM), and 8.5 million adults with diabetes are undiagnosed [1]. In 2020, there were nearly eight million adults discharged with DM [1]. One third of hospital admissions have a diagnosis of diabetes [2]. Adults living with diabetes are 3.1 times more likely to be hospitalized than those without diabetes [3, 4]. Patients with DM are often hospitalized for reasons other than diabetes [5]. Rubin performed a qualitative study including semi-structured interviews with patients with diabetes who were readmitted within 30 days of being discharged from the hospital. Risk factors for readmission included knowledge deficit related to diabetes and discharge instructions, ability to follow discharge instructions, and awareness of medication changes [6]. Factors that can significantly impact the cost of diabetes care may include increased length of stay (LOS), utilization of health-care services, and hospital readmissions [7, 8]. Inpatient costs related to diabetes account for \$97 billion annually in the United States [9]. Per capita hospital costs for people with diabetes were estimated to be \$4966 vs \$1202 for those without diabetes in 2017 [9]. In 2012, Center for Medicare and Medicaid Services started decreasing

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payments to hospitals for 30 day readmissions [6]. Prioritizing quality metrics to decrease 30 day readmissions and LOS have been implemented by hospitals to help decrease costs [10].

Hospitalized patients may lack knowledge of diabetes self-management skills such as understanding how and when to take their prescribed medications. Inpatient diabetes education is associated with reduction of 30-day readmissions [11–13]. Appropriate diabetes self-management education provided in the inpatient setting can lead to reduced health-care costs.

Inpatient Diabetes Education for Prevention of Errors

During hospitalization, patients can be at risk for adverse events including medication errors associated with insulin [14, 15]. National Inpatient Audit (NaDIT), a national assessment of hospital diabetes care, reported that errors frequently involved medications including insulin administration, hypoglycemia, and hospital acquired foot ulceration. Some examples of insulin errors include incorrect type of insulin given, insulin not signed off as given, and insulin given at the wrong time [16]. In 2014, The Institute for Safe Medication Practices (ISMP) conducted a survey of nurses and pharmacists, who ranked insulin ninth out of the 40 high alert medications. Insulin was ranked last for confidence that hospital precautions would prevent insulin errors [17]. The primary adverse event from insulin errors is hypoglycemia [17]. Insulin errors were identified as the most common type of medication errors in the ICU setting [18].

Risks associated with inpatient hypoglycemia include elderly age, type 1 diabetes, renal or hepatic insufficiency, hemodialysis, history of hypoglycemia, hypoglycemia unawareness, mismatch of insulin to meal delivery and blood glucose monitoring, poor oral intake or nil per os (NPO) status, short staff, and over treatment for hyperglycemia [19]. Health-care professional lack of knowledge regarding pharmacokinetics of insulin may contribute to inappropriate dosing and resultant hypoglycemia [20].

Hypoglycemia is defined by the American Diabetes Association (ADA) as a blood glucose <70 mg/dL [21]. Inpatient hypoglycemia is common with 25% of DM patients having an episode of hypoglycemia during their hospital stay [20]. Hospitalized patients on insulin have a greater than 2.5-fold risk for having a hypoglycemia episode during their hospital stay [22]. Normoglycemia in Intensive Care Evaluation—Survival Using Glucose Algorithm Regulation (NICE-SUGAR), a multicenter trial, showed that critically ill patients with moderate to severe hypoglycemia had 41% risk of death within 90 days of randomization [23]. Complications of hypoglycemia include a decrease in blood flow to the frontal lobe cortex of the brain and an increased risk of cerebral ischemia, stroke, and dementia [19]. Interventions that can impact reduction of inpatient hypoglycemia include education of health-care providers on identification of patients at risk for hypoglycemia, as well as signs, symptoms, treatment, and prevention of hypoglycemia [19].

Less than 50% of people with DM receive outpatient Diabetes Self-Management Education and Support (DSMES). In patients newly diagnosed with diabetes, less than 5% on Medicare and less than 7% with commercial insurance, use their DSMES benefit [24, 25]. The ADA and the Endocrine Society Clinical Practice Guideline state that inpatient diabetes education should focus on “survival skills” to safely transition inpatients to the outpatient setting [26, 27]. These include dietary recommendations, glucometer and blood glucose testing, and medication management such as injecting insulin.

Barriers to Inpatient Nursing Diabetes Education

DSMES is known to reduce the financial burden, prevent chronic complications, assist in lowering HbA1c, and improve quality of life [28]. Inpatient certified diabetes education and care specialists (CDCES) are trained to provide or oversee education given to patients and their families, review and update educational resources, assess and address barriers to care, help coordinate and support the patient through transitions of care, assist in the implementation of medication protocols for hyperglycemia and hypoglycemia treatment and prevention, and identify and develop quality performance improvement projects [16]. Providing diabetes education during hospitalization is very important; however, several barriers exist. Barriers include a lack of knowledge related to diabetes management, lack of confidence, lack of time to provide education, and a lack of inpatient CDCES staff [4, 29–31]. Diabetes management in the hospital is constantly changing. With informatics and technology advancing rapidly in health care, there is a knowledge deficit by professionals at the bedside [29]. This impacts quality of care as length of stay and readmissions are influenced. Knowledge deficits identified include pharmacokinetics of insulin, new treatments for diabetes management, technology, and personalizing glycemic targets [32]. Different assessment tools have been used to evaluate nurses’ knowledge of DM care and management in the hospital. One tool, the Modified Diabetes Basic Knowledge Test (MDBKT), identifies knowledge of hypoglycemia treatment, side effects of diabetes oral medications, and patient instructions regarding checking for urine ketones [31]. Another tool to assess nurse knowledge is the Diabetes Basic Knowledge Test (DBKT), which reported 70% of nurses had a low to moderate competence in diabetes in the United States [31]. Yacoub et al. created an educational program for nurses to address learning needs related to diabetes management. At the conclusion of the program, nurse scores increased from 52.7% pretest to 78.3% posttest. Areas with the largest rate of change were correct sites of insulin administration, insulin preparation, pattern of insulin administration and surgery, foot corn removal, and management of hypoglycemia [31].

Another barrier involves nursing confidence in diabetes knowledge to safely educate and care for patients in the hospital using survival skill methods and content [29]. In 2020, 19,783 CDCES were in practice. The amount of people with diabetes is expected to double every 15 years. There is one CDCES to 16,000 people with

diabetes [33]. Results from the 2021 Association of Diabetes Care and Education Specialists (ADCES) National Practice Survey showed that 23.8% diabetes care and education specialists work in the hospital setting [16]. ADCES identifies the value of CDCES as cost-effective and impacting improvement of clinical outcomes. However, despite these benefits, barriers to providing diabetes education to patients still exist including limited resources to support diabetes education and a shortage of CDCES [34]. CDCES have an impact on reducing length of stay, decreasing medication errors and improving patient safety, improving staff knowledge of diabetes management, and improving patient satisfaction [7]. In response, some institutions have developed diabetes education programs for health-care professionals to assist in providing diabetes self-management education to their patients.

Strategies to Provide Inpatient Nursing Diabetes Education

There is a limited number of CDCES working in the hospital setting, while the prevalence of diabetes is growing. Some urban hospitals have up to 30% of patients with a diagnosis of DM [2, 35]. Given the high prevalence, programs to provide education to bedside nursing professionals are warranted [36].

Various programs have been developed to address gaps in diabetes knowledge and confidence of staff to provide diabetes education at the bedside. The ADA and The Joint Commission (TJC) recognize that the success of these educational programs depends on the content of the education and that “program champions” are identified. Throughout the literature, there have been various names applied to these champions. Some have called them diabetes scholars, super-users, mentors, or champions [32, 35, 37]. They all conclude that these programs are effective in improving health-care professional knowledge of diabetes management and improve patient safety. Such programs have also become multidisciplinary to include providers, pharmacists, registered dietitians, physical therapists, exercise physiologists, podiatrists, ophthalmologists, and behavioral health specialists [33, 35].

Other tools have been developed to address the lack of knowledge, and confidence nurses have in teaching diabetes survival skills. Based on ADCES7 Self-Care Behaviors, CDCES throughout the Northwell Health System developed a handout entitled, “The 10 Knows for a Safe Diabetes Discharge (see Fig. 29.1) [16].” This tool is based on survival education skills and helps guide the bedside nurse on topics for patient education prior to discharge.

At Northwell Health, nurses and CDCES collaborated with an interdisciplinary shared governance body to develop a Diabetes Learning Needs Assessment Tool

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| <p>10 “KNOWS” for a Safe DIABETES Discharge</p> <p>This tool addresses important diabetes education points each patient should know prior to being discharged from the hospital.</p> <p>Nurses: please be sure to use the appropriate parameter on Sunrise to document the education you provide (i.e. “Diabetes Self-Management” parameter or “CPG Education” parameter).</p> <p>Patients: please ask questions if you are unclear about any of these topics. You should:</p> <ol style="list-style-type: none"> 1. (all) KNOW your type of diabetes (circle one): <ul style="list-style-type: none"> • Type 2 • Gestational • Other _____ 2. KNOW about hemoglobin A1C: <ul style="list-style-type: none"> • What it measures (2-3 month average of your blood sugar) • Your target A1C (circle one): ≤7 (general), 7-8 (if over 65 years old), other _____ • Your current A1C _____ 3. KNOW how to perform blood sugar monitoring correctly: <ul style="list-style-type: none"> • Blood glucose target (e.g. before meals, <180mg/dL 2-hrs after meals). • How to get your supplies, fill your prescriptions. • How to safely dispose of your sharps (i.e. lancets, pen needles, syringes, etc.). • Call your doctor if blood sugar >250mg/dL for more than 24 hours. • Be aware of hypoglycemia (blood sugar <70mg/dL). See #7 below. 4. KNOW the basics of a healthy diet: <ul style="list-style-type: none"> • The importance of having meals and snacks on time, and not skipping meals. • The importance of eating meals and eating consistent carbohydrate. Example: Use the plate method: ½ plate salad/vegetables, ¼ plate protein, ¼ plate carbohydrates. • Avoid sugary drinks and snacks. • The importance of following up with a dietitian. Ask about the Northwell's Healthy Living Program Diabetes. Call 855-864-6257 for enrollment. 5. KNOW how and when to take your diabetes medication: <ul style="list-style-type: none"> • Importance of taking your medication as prescribed (e.g. take metformin with meals). • Call your provider for possible medication adjustments when not eating. • How to get your medication, fill your prescriptions. • Not taking your medications can raise your blood sugar. | <p>10 “KNOWS” for a Safe DIABETES Discharge</p> <p>6. KNOW how to safely administer insulin (if needed): <ul style="list-style-type: none"> • Using insulin pen, or vial and syringe. • Time and dosage(s) of your insulin(s). • Never mix Lantus or Levemir with any other insulin in a syringe. </p> <p>7. KNOW about hypoglycemia (blood sugar <70mg/dL): <ul style="list-style-type: none"> • Common signs and symptoms: fast breathing, shakiness, sweating, chills, irritability. • Treat with the 15/15 Rule: take 15 carbs, wait 15 minutes, re-check blood sugar. Repeat if hypoglycemia continues. Examples of 15g carbs: 4oz juice or regular soda, 3-4 glucose tablets, 1 tube glucose gel, 1 tablespoon sugar/honey, 8oz skim/1% milk. • How to use glucagon if needed (family member given instruction). • Activity/exercise can lower your blood sugar. </p> <p>8. KNOW “Sick day rules”: <ul style="list-style-type: none"> • Importance of continuing to take your diabetes medications appropriately. • Drink fluids to prevent dehydration (e.g. Gatorade G2). • Monitor blood sugars every 4 hours. • How and when to perform ketone testing. • When to call the doctor (e.g. if blood sugar continually <70mg/dL, or >250mg/dL, if you feel known, nausea, vomiting, temp >101°F, if unable to swallow or drink liquids). </p> <p>9. KNOW the importance of following up with your Provider(s) about your diabetes: <ul style="list-style-type: none"> • Keep your appointments. • Contact Provider when you have questions/concerns. • Your doctor's name _____ and telephone # _____ • Your next appointment date _____ and time _____ </p> <p>10. KNOW the diabetes resources available to you after discharge: <ul style="list-style-type: none"> • Wellness classes held at various locations. Call 855-364-6257 for details. • Diabetes American Diabetes Association website: diabetes.org. American Association of Diabetes Educators website: diabeteseducator.org for patient education materials </p> <p style="text-align: center;"><small>Kaypowski et al 2012 JGIM, reprinted with permission</small></p> |
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Fig. 29.1 10 “Knows” for a Safe Diabetes Discharge

based on the “10 Knows” checklist (Fig. 29.2). This tool took four content areas from the “10 Knows” that focused on medication(s), meals, movement (activity), and monitoring (including signs, symptoms and treatment of hypoglycemia). The use of this tool helped assess learning needs of the patient and increased nursing confidence in providing diabetes education [38].

Some hospitals have developed other tools to help the bedside nurse provide diabetes education. A “diabetes to go” program delivers education using a web-based approach [24, 39]. Patients had to answer 15 questions on survival skill education. If they got questions wrong, this would prompt them to watch a video on the topic. The videos were 3–6 min long. The program recorded the patient’s answers and the videos they viewed. The limitations of this program were that the information presented was at a high literacy level, it was only in English, some of the videos were too long, and nurses wanted a better understanding of what to teach the patient [24]. To address the lack of time, some programs have implemented the use of tablets to provide diabetes education at the bedside [25].

| Diabetes Assessment Tool | | | |
|--|---|--|--|
| Initials: _____ | Pre-teaching date: _____ | Post-teaching date: _____ | |
| Room # _____ | Phone # for follow-up call _____ | | |
| Re-evaluate before discharge. | | | |
| <u>Meds</u> | Pre-Educ. Y/N <input type="checkbox"/> | Post-Educ. Y/N <input type="checkbox"/> | |
| What type of diabetes do you have? | | | |
| What meds do you take (name, dose, and frequency)(Type 1 MUST be on insulin) | <input type="checkbox"/> | <input type="checkbox"/> | |
| What time of day do you take your meds in relation to meals? (1/2 hr before for po meds, immediately before for insulin) | <input type="checkbox"/> | <input type="checkbox"/> | |
| If insulin, are you comfortable drawing it up and injecting it? Where do you inject it? (Fatty tissue) | <input type="checkbox"/> | <input type="checkbox"/> | |
| <u>Move</u> | | | |
| How does physical activity affect your blood sugar? (Keeps it down) | <input type="checkbox"/> | <input type="checkbox"/> | |
| Should you exercise before or after meals? (After eating) | <input type="checkbox"/> | <input type="checkbox"/> | |
| <u>Meals</u> | | | |
| What are your eating habits? | | | |
| • At least 3 meals | <input type="checkbox"/> | <input type="checkbox"/> | |
| • Snack at night. | <input type="checkbox"/> | <input type="checkbox"/> | |
| • Consistent meal times | <input type="checkbox"/> | <input type="checkbox"/> | |
| Why shouldn't you skip any meals? (Hypoglycemia) | <input type="checkbox"/> | <input type="checkbox"/> | |
| <u>Measurement</u> | | | |
| How often do you check your blood sugar? | <input type="checkbox"/> | <input type="checkbox"/> | |
| When/What times? (AC and before bed for IDDM; before bkfst and 2 hrs after dinner for NIDDM) | <input type="checkbox"/> | <input type="checkbox"/> | |
| What is your numbers goal? (80-130 pre-meal; <180 2 hrs post meal). | <input type="checkbox"/> | <input type="checkbox"/> | |
| Do you know your A1C? (RN ck. w/provider if don't know or answer is out of range) | <input type="checkbox"/> | <input type="checkbox"/> | |
| How do you know if your sugar is too low? (Patient states 1-2 symptoms of hypoglycemia) | <input type="checkbox"/> | <input type="checkbox"/> | |
| What do you do when that happens? (15/15 rule; 4 oz. apple juice, 4 glucose tabs, 1 tube glucose gel, etc. re- ✓. Fs in 15 min. NO candy, milk, cookies, cake, etc.) | <input type="checkbox"/> | <input type="checkbox"/> | |
| Follow up date: _____ Initial: _____ | A. Hasse | | |

Fig. 29.2 Diabetes assessment tool

Provider Education

Diabetes is a highly complex disease requiring close coordination of care including appropriate diagnosis, education, treatment, prescribing, and follow-up. Glucose variability in hospitalized patients is associated with adverse events, including death

[40]. The ADA recommends specialized glucose monitoring or diabetes care teams. The benefits of such teams include decreased LOS, decreased readmissions, and improved glycemic control, with reduction of hypoglycemia rates. This type of team does not replace the primary attending or team's knowledge and coordination of care but supports them [40]. Many hospitals may not have the resources to provide such a specialized team. Or many hospitals may have a very vast and large patient population that having a glycemic team may only affect the more difficult patient cases. Therefore, many patients are managed by primary hospitalists, residents, or advanced care provider teams to diagnose, educate, treat, and transition care to the primary care provider in the outpatient setting. Given that diabetes is a complex, layered disease, the primary teams would need to have an adequate comfort level knowing patient's type of diabetes, how this is diagnosed, insulin management including several types of insulin and the pharmacological science to each insulin type, oral medication therapies, non-insulin injectable therapies, medical nutrition therapy, insurance barriers to prescribing for outpatient management, and finally what does the patient need to learn in order to implement basic survival skills once the patient has left the hospital. The hospital primary care teams require the knowledge, skill, and equipment to provide the patient with safe diabetes self-management care [37].

Hyperglycemia in the hospital setting can be attributed to many factors. This includes stress hyperglycemia in a non-diabetes patient during acute illness and steroid-induced hyperglycemia and those patients with undiagnosed diabetes. Hyperglycemia is poorly controlled as providers feel uncomfortable, unfamiliar, and hesitant to initiate insulin therapy due to fear of hypoglycemic events [41]. Basal bolus insulin therapy (long-acting insulin and rapid-acting insulin prior to meals) is the preferred method to control hyperglycemia. Because insulin dosing is patient-specific, this is perceived to be a very complex guideline [42]. Many hospitals do not have the resources to employ a full-time endocrinologist for inpatient glycemic management. Residents and advanced care providers (PA/NP) learn from their attendings or when there is access to endocrinology consultants on a case-by-case basis. Some residents may choose to rotate with an endocrinologist. With this learning model, diabetes management is adopted based on their hospitalist's own knowledge, comfort, and readiness to teach inpatient glycemic management.

Goals of inpatient management are very different from those for outpatient management. Hospital blood glucose targets are higher with a goal of 110–180 mg/dL in non-critically ill patients [26]. Outpatient guidelines have a target BG 90–140 mg/dL [40]. Several studies have shown that strict glycemic management places patients at risk for more hypoglycemia events, increased LOS, and poor outcomes. In addition, patients are not in their usual “healthy” state; nutritional intake is often altered, and unlike the patient's home diets, some of the diabetes medications are contraindicated for testing that uses contrast dyes. Blood transfusions, fluids, or parenteral nutrition can impact blood glucose levels as well.

Like most disease-specific education, teaching methods vary. Northwell Health developed a full-day educational course for providers that includes background pathophysiology, oral medications, non-insulin injectables, insulin, insulin

pumps, glucometers and continuous glucose monitors, glycemic pattern management, insurance concerns, nutrition, transitioning care to the outpatient setting and a hands on, interactive component utilizing insulin pens, glucometers, non-insulin injectables, and insulin pumps. This can be done several ways. The COVID pandemic has pushed forward technology and web-based classrooms, meetings, and conferences. This gives an opportunity to have more attendance with virtual education. The drawback is skills such as in person demonstration of insulin pen cannot be practiced. However, there are programs with visual aids where the learner can interact with a step-by-step answering process. The learner cannot proceed until all steps are placed in the correct order. A randomized controlled trial concluded that web-based diabetes training programs were effective at increasing diabetes-related knowledge and skills [43]. Other methods include the standard didactic education with skills practice and offering a clinical rotation with an inpatient diabetes team member such as certified diabetes educators, advanced care providers, and/or physicians.

The Joint Commission offers an advanced disease-specific care certification for inpatient diabetes care. TJC requires providers to have specific education, training, and experiences on an ongoing basis. This has positively impacted length of stay and reduced readmissions, hypoglycemia, and hyperglycemia [44].

A 2017 review of educational interventions found that glycemic management knowledge can be improved with learners who are active and participatory, that education on glycemic management must reach a large audience of learners, and that institutions should adopt education for glycemic management as an official component of hospital quality improvement [45]. Computer-based learning activities, live workshops, lectures, clinical rounds, and interactive activities were approaches used. Outcomes of such interventions include reduction of management errors, more frequent use of basal and bolus insulin, reduction in use of sliding scale insulin, improved frequency of foot assessment, reduced length of stay, reduced severe hyperglycemia, more blood glucose values in target range, and improvement of hemoglobin A1c levels after discharge. Drawbacks of the educational interventions included decline in knowledge with time from education, decline in confidence in more complex tasks, and increased rates of hypoglycemia [45].

There are several challenges to providing relevant diabetes education to providers. There are financial implications such as adequate staffing so others can have time to be educated or attend educational rounds in diabetes care. Having an educational program designed to improve care for the inpatient diabetes population would have to be supported by the leadership of an institution. In order for this to happen, financial incentive to obtain buy-in from leadership would have to be proposed. The goal is to decrease rates of hypoglycemia, hyperglycemia, length of stay, and readmission. By improving these metrics, health-care costs can be reduced.

Effect of Diabetes Education on Length of Stay

Hyperglycemia and hypoglycemia are contributing factors to prolonged LOS [9]. Hospitalized patients with congestive heart failure (CHF) and persistent hyperglycemia have an increased LOS (8.1 days) compared to those with CHF without hyperglycemia (5.2 days) [46]. Garg et al. found that every hospital day with hypoglycemia led to an additional 2.5 day increase in LOS [47]. Therefore, targeting educational initiatives to decrease hyper- and hypoglycemia can have an impact on LOS.

At Johns Hopkins Hospital, an interdisciplinary glucose steering committee (members included diabetes clinician, endocrinologist, hospitalist, house staff, mid-level providers, nurse educators, pharmacists, dietitians, and point-of-care testing (POCT) laboratory personnel) was created to decrease rates of hypo- and hyperglycemia [37]. This committee developed an educational program for nurses, which included a diabetes superuser program led by a nurse practitioner and certified diabetes educator (now known as CDCEs). Nursing education was provided by learning modules, providing continuing education credits to nurses, development of “Nursing In-Service-In-A-Box (where superusers presented one of the cases discussed at nursing rounds), and nursing support for diabetes education (focusing on survival skills). An 18.8% decrease in hypoglycemia rate showed an important outcome of the superuser program [37].

While A PubMed search yielded few results specifically looking at diabetes education and LOS, some research has been performed looking at the impact of a diabetes management service (including a team approach to diabetes care with both clinical endocrine providers and certified diabetes educators) on LOS. In a retrospective study, Mandel et al. found that the LOS for patients cared for by a diabetes management service was decreased by 27% [48]. Earlier referral to diabetes management service showed a decrease in LOS compared to patients referred closer to discharge (4.7 vs 6.1 day, respectively) [49]. A retrospective study looking at inpatient education for patients with diabetes found that a specific diabetes education pathway called DICE (diabetes inpatient care and education) found a reduction in LOS for patients studied. Their study included specific education guidelines for patients and education for physicians. Education was accomplished by increasing diabetes educators [50].

Effect of Diabetes Education on Readmissions

Hospital readmission is an unscheduled hospital admission where a patient returns to the emergency department for observation and care within 30 days of their last discharge. Having a primary or co-morbid diagnosis of diabetes may be a contributing risk factor for hospital readmissions [51]. In the United States, the Hospital Readmission Act of 2012 has fined hospitals who have increased readmission rates.

The annual cost of 30-day readmissions is \$20–25 billion [9]. Decreasing hospital readmission is a priority across the national health-care system to reduce cost and improve care.

Jiang et al. showed that about a third of hospitalized patients with diabetes had an increased risk of readmissions in the following year [52]. Some causes for this increase in readmission include lack of knowledge of diabetes and medication adherence [9]. A retrospective study looking at 30-day readmission rates showed that implementation of a diabetes resource nurse (DRN) program (diabetes champion program) decreased rates [53]. Drinic et al. compared 30 day readmission rates of patients receiving care by a DRN versus patients receiving care by a staff nurse. After the program was implemented, the 30-day readmission rate for patients educated by DRN was 18% versus 21.3% for those cared for by a staff nurse ($p < 0.0001$) [53]. However, the most significant impact on decreasing readmissions was for patients seen by CDCES, with a 30 day readmission rate of 15.1% ($p < 0.0001$) [53].

Other studies similarly conclude that 30-day readmission rates improve when proper diabetes-specific education was taught to the patient before discharge [11].

Other investigations regarding DM and LOS have looked at the impact of a service or team approach effect on readmission rates. Both LOS and readmission rates decreased when hospitalized patients were closely evaluated and followed by a diabetes management service [48]. Mandel et al. reported a reduction of 10.71% in readmissions when patients were managed by a specialized diabetes team while inpatient [48]. More research would be beneficial in further examining the direct relationship between formal inpatient diabetes education and 30-day readmission rates. Potential solutions that have been suggested for improving these metrics include a bundled multidisciplinary approach, such as specific discharge medication counseling [9], inpatient diabetes education, and facilitation of support for transitioning of care such as scheduling with outpatient providers.

Conclusion

The prevalence of DM in the hospital is growing. It has been reported that only 50% of people with diabetes receive DSMES and less than 5% newly diagnosed with diabetes, on Medicare, use their DSMES benefit. Therefore, the inpatient setting might be the only education patients receive. Since only a small percentage of CDCES work in the inpatient setting, it has become increasingly important to hospitals to have “champion programs.” These programs are beneficial in increasing provider and nurse knowledge of diabetes, preventing medication errors, improving the management of diabetes in the hospital, and increasing their comfort level in providing diabetes education. Inpatient diabetes education may influence reduction of LOS and hospital 30-day readmissions. Inpatient diabetes education has a major impact on improving patient safety, and the financial burden hospitals are facing in taking care of this vast patient population.

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Chapter 30

Barriers to Diabetes Care at Hospital Discharge



Caitlyn Gordon, Hannah Nelson, and Karina Perez-Vilbon

Introduction

Transitions of care (TOC) is the movement or transfer of a patient from one setting to another [1]. Poor transitions of care from the hospital to home can lead to adverse events, readmissions, delays in care, increased healthcare costs, patient and provider dissatisfaction, and morbidity and mortality [2]. Medication errors or unintentional medication discrepancies occur in about 50% of adults after hospital discharge, and about 20% of patients experience adverse drug events [3–7]. Nearly 75% of adverse drug events are preventable, and one of the most common classes of medications reported to cause adverse drug events is antidiabetic medication [3, 7].

In 2018, out of 19 million hospital admissions in the United States, over eight million were in patients with diabetes mellitus (DM) [8]. One of the largest contributors to the cost of diabetes is inpatient hospital stays, costing \$69.7 billion in 2017 [9]. At baseline, patients with DM have a higher readmission risk compared to patients without diabetes, 14.4–22.7% versus 8.5–13.5%, respectively; Ostling et al. reported readmission as high as 24.3% with the most common cause of readmission being infection [10]. Risk factors for 30-day readmission include comorbidity burden, public insurance, insulin therapy, lack of an outpatient visit after

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discharge, hospital length of stay, prior discharge within 90 days, race/ethnicity, among others in patients with diabetes [11–14].

Hospital discharge planning is a national priority and is included in the Joint Commission's 2022 National Patient Safety Goals® as well as the Advanced Certification Requirements for Inpatient Diabetes [15, 16]. These requirements stress the importance of proper discharge planning, written discharge instructions, provider handoff, and an updated medication list [4, 15, 17]. Transition from the hospital to home is recognized as a high-risk scenario, which is why hospital discharge is one of the most vulnerable times for a patient and, if not done properly, can lead to adverse events [18]. This chapter will focus on the transition home from the hospital for patients with diabetes including barriers and pitfalls, as well as strategies to overcome transitions of care challenges. Most of the concepts presented in this chapter relate to all types of diabetes; however, mention of non-insulin agents is strictly for type 2 diabetes.

Challenges to Safe and Effective Discharges

Referring to Table 30.1, practice case 1, on admission, several challenges are presented including new change in cognitive status (A&Ox2), history of cerebrovascular accident (CVA) with right-sided hemiparesis, and new, uncontrolled T2DM (HbA1c 12.1%). Although the patient is not admitted specifically for diabetes, the

Table 30.1 Case studies

Case 1 SM is a 72-year-old female who was admitted to the hospital for urinary tract infection and hyperglycemia. She is alert and oriented x 2 (baseline is alert and oriented x 4). Her past medical history is significant for hypertension (HTN), hyperlipidemia (HLD), cerebrovascular accident (CVA) with right-sided hemiparesis, and type 2 diabetes (T2DM). Home medications include lisinopril 5 mg daily, atorvastatin 10 mg daily, and metformin 500 mg daily. She does not know how to check her blood sugar; she gets it checked every 3 months at the primary care office. Patient's hemoglobin A1c (HbA1c) is 12.1%.

Case 2 JP is a 41-year-old female with a history of T2DM (A1c 11.3%) and asthma who presents to the hospital with bilateral ear pain. She has been admitted multiple times for various reasons in the last few months. Her preferred language is listed as English. However, after asking the patient to read the education handout, it is discovered she has limited English proficiency and Spanish is her preferred language. Upon discharge, her pharmacy only dispensed basal insulin because her insurance formulary did not cover the bolus insulin prescribed. The patient thought that it meant her diabetes was improving since she only received one insulin and not both.

Case 3 Patient MK is a 65-year-old obese male with a history of HTN, HLD, and benign prostatic hyperplasia. Patient was admitted to the emergency short stay unit for hypertensive crisis. HbA1c was 9.5%, consistent with newly diagnosed T2DM. Patient was seen by endocrinology and recommended to be discharged on a basal insulin and an oral regimen. Patient was taught how to administer insulin via pen. Patient was (accidentally) prescribed insulin vial, insulin pen needles, and a glucometer, which were all picked up from the pharmacy. However, the patient was seen in the emergency department again 24 h later, reporting he cannot use the insulin vial or glucometer

primary team needs to think about optimizing her diabetes regimen upon admission, including the addition of insulin or once weekly glucagon-like peptide-1 agonist (GLP-1). One major question is can the patient learn to self-administer an injectable medication and check her blood glucose due to the right-sided hemiparesis? If not, the team needs to determine *who* will learn to administer an injectable medication and check her blood glucose versus using a less effective oral regimen. This section will focus on the challenges that need to be addressed to achieve a safe and effective discharge from the hospital.

Acute changes in a patient's condition are one of the earliest challenges that may present itself in the inpatient setting. Patients may be admitted to the hospital with new, worsening, or unaddressed visual or hearing difficulties, delirium, falls, dexterity issues, depression or mental health conditions, urinary incontinence, and/or renal impairment [19, 20]. Early in the hospital admission may not be the optimal time for learning if their change in condition is temporary and expected to improve. For example, in case 1, the patient is an older adult with a urinary tract infection experiencing delirium; she may return to her cognitive baseline as the infection improves. Additionally, patients who are experiencing temporary side effects of medications (e.g., sedation or delirium secondary to anesthesia or opioids) may need to be taught once they are off certain medications and/or back to baseline [21, 22]. In other scenarios, however, if this is the patient's new baseline, it can pose challenges to safely discharge a patient home if the primary team does not address this early during the hospital stay. Families or caregivers should be involved to help with early initiation of a safe discharge plan home [23].

Communication breakdown regarding patient education is a challenge to a safe and effective discharge (Table 30.2). Patients who must be identified early in the

Table 30.2 Barriers to safe and effective discharge

| Patient-specific | Institution/provider-specific |
|--|--|
| <ul style="list-style-type: none"> • Unwilling or unable to participate in education or discharge planning • Acute (or chronic) physical or mental health conditions • Social determinants of health <ul style="list-style-type: none"> – Financial barriers (e.g., uninsured or underinsured) – Lack of transportation (e.g., to appointments) – Lack of social support – Low health literacy/numeracy • Poor recall of health information • Lack of self-efficacy • Loss of control over chronic illness/diabetes distress • Not understanding importance of medications • Complexity of treatment • Mismatch in provider and patient expectations | <ul style="list-style-type: none"> • Shorter hospital length of stay—insufficient time for transitional planning/education • Lack of communication • Lack of accountability/unclear responsibilities of team members • Lack of standardized education • Medication reconciliation errors and discrepancies (e.g., missing diabetes supplies) • Incomplete discharge paperwork (e.g., missing diabetes-related instructions) • Pharmacy-related issues (e.g., prior authorization, high cost, etc.) • Lack of handoff with outpatient provider • Lack of follow-up appointment (or distant appointment date) • Failure to initiate or intensify diabetes treatment (clinical inertia) |

admission process include: patients who have a new diagnosis of diabetes, patients who are new to insulin or have changes to their home medication regimen, and patients who are new to self-monitoring blood glucose levels [24]. Day of discharge is not appropriate for education and skills demonstration. At many institutions, it may not be clear who is responsible to educate the patient and what exactly should be taught, especially if there aren't dedicated team members or resources for diabetes education [25, 26]. Knowledge deficiencies in diabetes care (among nurses), variability in diabetes education provided, and inadequate duration of education are all causes of poor transitions [27, 28]. Communication breakdowns on the part of the primary team can include not informing the appropriate team member (e.g., nurse, certified diabetes care and education specialist (CDCES), registered dietitian) that the patient in question needs diabetes education, particularly if diabetes isn't the reason for admission. Ineffective physician-patient communication occurs due to reliance on verbal instruction, use of medical terminology, and the use of closed-ended questions to assess patient understanding [4]. In general, about 40–80% of medical information provided by healthcare providers is forgotten immediately, and about half of the information that is remembered is incorrect [29]. Patient recall about diabetes management specifically from their inpatient stay may be limited [30].

Inpatient length of stay for diabetes has decreased over the last 30 years from 9 to approximately 5 days; along with greater practitioner and nursing workload, time constraints, and competing priorities, this can add to rushed discharges and insufficient time for inpatient education and discharge planning [8, 20, 23, 31]. Discharge paperwork may not have diabetes-specific instructions including who to contact, and it may have inadvertent medication discrepancies (omissions, duplications, errors); this can lead to adverse events and/or overutilization of the emergency department [7, 32].

Patient-specific barriers are numerous and can include financial difficulties, lack of transportation, lack of social support, low health literacy/numeracy, lack of confidence or self-efficacy, loss of control over chronic illness/ability to care for oneself, diabetes distress, mental health conditions, forgetfulness, and not understanding the importance of medications, among others (see Table 30.2) [14, 32–34]. Patients with diabetes have higher out-of-pocket healthcare and prescription costs compared to patients without diabetes [35]. Because diabetes disproportionately affects racial and ethnic minorities as well as low-income populations, high medication costs can pose a challenge to safe discharges [36]. Education-wise, health literacy impacts a patient's ability to understand their health and make decisions. Low health literacy is more common in older adults, minority populations, non-English speakers, and in patients with low socioeconomic status [37, 38]. Higher health literacy and self-efficacy (a person's confidence in their ability to perform health behaviors successfully) are both associated with improved self-management [39–42]. Low health literacy and numeracy can make it difficult for patients to manage their diabetes, understand medication directions or adjustments, interpret their blood glucose values, and make dietary adjustments [43]. One study reported that low health literacy in patients with diabetes was a contributor for 30-day readmission; patients in this

study couldn't recall current medications, follow-up care, or other instructions from the previous hospital stay [32]. Limited English proficiency (Table 30.1) in general is associated with decreased understanding of medical information and in type 2 diabetes and is associated with longer hospital stays and poorer glycemic control [44]. Lastly, culturally, there may be negative or preconceived perceptions about starting certain medications, such as insulin [45]. Patients and their families may have significant fears, including about side effects, needles, organ damage, or other harm. There may be concerns about complexity, inconvenience, embarrassment, cost, or view insulin as a punishment [45, 46].

Medication-related issues can pose a barrier to safe discharge [32, 47]. More than half of patients discharged have at least one or more unintended medication discrepancy with nearly 40% of them having the potential to cause moderate to serious harm [7, 48]. Many of the errors are omissions of regularly used home medications, which can be prevented by obtaining an accurate medication history on admission [48]. One survey study reported 20% of patients discharged with diabetes had difficulty obtaining their diabetes medications and supplies [49]. Unlike other disease states, there can be multiple medications and supplies that are needed including glucometer, test strips, lancets, alcohol swabs, insulin syringes or pen needles, glucagon, ketone strips, and others [20]. Providers may not be familiar with every supply necessary and can inadvertently forget to prescribe vital supplies. A small observational study found that providers inappropriately prescribed diabetes supplies on discharge 47% of the time. About 29% of errors were due to missing supplies such as pen needles or syringes [50]. Table 30.1 clearly demonstrates prescribing the incorrect dosage form of insulin (vial instead of pen) along with missing supplies for the insulin and glucometer. Unbeknownst to the provider, prescriptions sent to the pharmacy may need prior authorizations or step therapy first, may need to be switched to a formulary alternative, may not be affordable (e.g., due to deductible, donut hole), or may not be in stock [14, 34, 51]. Low-income patients on high deductible plans are particularly at risk for readmissions [52]. Medications requiring a prior authorization can delay discharges, negatively impact adherence, or increase the risk of adverse drug events post-discharge [53]. Additionally, diabetes supplies may need prior authorization or may have quantity limits [32, 51]. For pharmacy-related issues, the pharmacy may not have the patient's correct insurance, or the patient's insurance may have lapsed, the pharmacy may be closed when the patient is discharged, the pharmacy may not be able to contact the inpatient provider, or the medication may be out of stock or on backorder. In a patient prone to diabetic ketoacidosis, inability to pick up basal insulin can be life threatening.

Failure by providers to optimize or initiate diabetes treatment upon discharge occurs frequently, known as clinical inertia [34, 54, 55]. This could be due to time constraints, lack of familiarity with newer diabetes agents, or wishing to defer to the patient's outpatient provider [34]. There is evidence that optimizing diabetes regimens in patients with uncontrolled HbA1c can lead to fewer readmissions and improved glucose control [33, 56]. In a large pharmacy claims study, 83% of patients with DM were on antidiabetic medications inpatient, but 60% did not have a

pharmacy claim for any antidiabetic agent within 30 days of discharge [54]. The authors postulated that this could be due to providers failing to initiate or intensify regimens upon transition home since the number of patients with a pharmacy claim for diabetes agents was less after hospital discharge compared to before hospitalization [54]. In patients admitted with HbA1c greater than 8%, only 22.4% of patients had a change in therapy upon discharge, and almost one-third had no change in therapy or scheduled follow-up within 30 days [55].

Other care barriers include lack of insurance, lack of a primary care provider or endocrinologist after discharge, and distant appointment dates [14, 23]. Underutilization or delayed home healthcare services after diabetes-related hospitalizations is associated with greater odds of 30-day hospitalization [57]. Work, home, or caretaker responsibilities along with transportation or financial barriers may make it difficult to get to the appointments [14, 32]. Fifty percent of patients discharged from an urban hospital reported barriers to keeping discharge appointments, namely, due to transportation and financial barriers (e.g., no insurance) [58]. There may be long wait times to get an appointment with an endocrinologist or no offices near their home [34]. Lack of proper handoff or access to hospitalization records between the inpatient and outpatient provider can also lead to poor transitions of care and even overutilization of the emergency department when the patient isn't sure who to contact post-discharge (case 3) [7, 23].

Strategies to Overcome Challenges

There is no one-size-fits-all approach to a safe and effective discharge. Discharge planning, needs assessment, and treatment-related burden screening should begin on admission (or as early as possible) [34, 59–61]. The primary team should adapt and update the discharge plan as the patient's needs change, preferably in a prominent location in the electronic health record (EHR). One of the earliest interventions to help with discharge planning is to ensure an admission HbA1c is drawn if one is not available from the last 2–3 months [17]. Having a hospital discharge algorithm based on admission HbA1c has been proven to be helpful in optimizing treatment regimens and improving blood glucose control [17]. Table 30.3 summarizes a variety of strategies that can be used to improve transition of care for patients with diabetes at hospital discharge.

In case 1, discharge planning needs to begin shortly after admission to address each barrier. Interdisciplinary teamwork becomes vital for this patient as she works with physical and occupational therapy, as well as her nurses and potentially a diabetes care and education specialist. Family should be involved early in the admission in the event they need to administer injectable therapy and check fingersticks due to her right-sided hemiparesis. If the family makes known that four injections per day (basal/bolus insulin) is too much, alternative treatment plans can be made well before discharge [14, 33]. For example, the family agrees to one injection per

Table 30.3 Strategies to safely transition patients with diabetes home

| IDENTIFY & ADDRESS SPECIFIC BARRIERS AS THEY ARISE | | |
|---|--|--|
| MEDICATION-RELATED STRATEGIES | PATIENT-RELATED STRATEGIES | POST-DISCHARGE STRATEGIES |
| <ul style="list-style-type: none"> Reconcile home diabetes medications with discharge medications (adjust regimen based on patient's glucose control, comorbidities, and patient feedback/ability) Electronically prescribe medications and supplies early to address any unanticipated issues (e.g., prior authorization, formulary changes, cost concerns, medications out of stock) Computerized order sets or favorites list for diabetes supplies Ensure patients are aware of and agreeable to cost and treatment plan If patients cannot afford medications and/or supplies, consider less expensive alternatives (e.g., generic medications, coupons, patient assistance programs) and refer to appropriate resources Consider implementing a Meds-to-Beds program Utilize transition of care pharmacists | <ul style="list-style-type: none"> Start education and needs assessment early (involve family or support persons where appropriate) Screen for social determinants of health and refer to proper resources for support (social work/case management) Use diabetes champion program and delegate roles and responsibilities among different team members Ensure survival skills are understood and can be taught back by the patient (blood glucose monitoring and glycemic goals, hyper- and hypoglycemia recognition and treatment, healthy food choices, antidiabetic regimen for discharge, sick day management, and proper use and disposal of needles/syringes) Utilize return demonstration of diabetes devices (e.g., insulin pens) Provide education in patient's preferred language and supplement with material to take home (written or video aids) | <ul style="list-style-type: none"> Ensure the patient has a detailed and structured written discharge plan including who to call for questions Proper handoff with the PCP and/or endocrinologist Visiting nursing services (especially for new diagnosis) Schedule outpatient follow-up when possible with PCP, endocrinology, and/or CDCEs within one month <ul style="list-style-type: none"> The specifics of the appointment should include appointment date, time, location, phone number, and provider name Consider telehealth appointments for improved access to care or 2-3 day phone call follow-up to address questions or concerns Consider implementing a previously studied transitions of care model (CDCEs, NP, pharmacist-led) which includes post-hospital phone calls or office follow-up, education, and/or provider handoff |

PCP primary care provider; CDCEs certified diabetes care and education specialist; NP nurse practitioner

day (basal insulin) plus one injection per week (GLP-1 agonist) as well as to place a continuous glucose monitor on the patient every 10–14 days. The patient is then able to learn how to monitor her blood sugar using the continuous glucose monitor, and the family can have remote access when they are at work or away from the patient [34].

Medication Reconciliation

Medication reconciliation is vital to ensure all home medications are accounted for (continued, discontinued, or dose changed) [60]. All new or changed medications need to be sent to the pharmacy in a timely manner, and the provider or other health care team member should follow up to ensure previously discussed issues (e.g., coverage, cost) are resolved prior to the patient leaving the hospital [14, 34]. Sending discharge prescriptions more than 24 h prior to discharge has shown to decrease inpatient length of stay [62]. Transitions of care pharmacists have aided in identifying potential medications (including diabetes medications) that may need a prior authorization and have improved time to prior authorization approvals and prevented delays in discharge; they have also helped identify and resolve medication discrepancies prior to patient discharge [53, 63]. Executing a “Meds to Beds” program, such as with an on-site outpatient pharmacy, could ensure any

discharge prescription issues are addressed prior to patient discharge and could improve patient satisfaction; however, it has not been shown to decrease 30-day readmissions, and patients with diabetes have not been targeted in studies to date [64–67]. Diabetes supplies also need to be sent to the pharmacy (or appropriate location such as a durable medical supplier). Implementing a computerized favorites list for diabetes supplies has shown to help prescribers appropriately prescribe them and decrease inadvertent omissions [50]. Prior to discharge, patients should be aware of the pricing of medications and/or supplies and asked if they are able to afford and adhere with the treatment plan; if not, they should be referred to appropriate resources and/or provided with less expensive alternatives (e.g., generic medications, coupons, patient assistance programs) [34]. In conjunction with medication reconciliation, patients should be called 2–3 days after discharge to identify any discharge discrepancies, to address any patient or family member concerns, and to review medicines, appointments, and who to call if an issue arises [7, 68].

Optimizing Diabetes Medications upon Discharge

Often, in the inpatient setting, insulin is the preferred treatment option regardless of whether a patient will be discharged on insulin. The American Diabetes Association (ADA) and American Association of Clinical Endocrinology (AACE) recommend resuming oral medications 1–2 days prior to discharge [60, 61, 69]. For patients with uncontrolled diabetes, intensification of the outpatient regimen while minimizing the risk of hypoglycemia is positively associated with decreased readmission and improved glucose control [33, 56]. Umpierrez et al. tested an algorithm whereby patients with HbA1c 7–9% were discharged on their home oral regimen plus 50% inpatient basal dose and patients with HbA1c >9% were discharged on their home oral regimen plus 80% of the inpatient basal or basal-bolus regimen. Patients with HbA1c <7% and no hypoglycemia were restarted on their outpatient regimen [17]. Donihi adds to the previous study's approach and recommends intensifying based on the number of non-insulin home therapies, maximizing home doses (where applicable) and incorporating newer agents (like GLP-1 agonists) [33]. GLP-1 agonists and SGLT-2 inhibitors may be indicated at discharge to optimize not only diabetes but comorbidity management such as cardiovascular disease, chronic kidney disease, and/or heart failure [61]. Demidowich et al. offer a simple strategy of recommending one non-insulin medication (based on efficacy and/or cost) for every 1%, the patient's HbA1c is above target [34]. In older adults, those with poor adherence, or in patients with significant barriers to frequent dosing, it may be more prudent to avoid complex diabetes regimens, polypharmacy, and/or hypoglycemia-causing medications, which may assist with safe discharges and prevent readmissions [14, 19, 34].

Structured Discharge Communication

A structured discharge plan has been shown to reduce inpatient length of stay and readmission rates in older adults [70]. Along with proper medication reconciliation, all medication updates should be clearly written out and described to the patient, family, and/or caregiver in their native language, as appropriate [12, 15]. Verbal discharge instructions alone are insufficient. When diabetes isn't the reason for admission, it can be overlooked in the discharge paperwork [71]. The discharge document should include type of diabetes, patient's admitting diagnosis and problem list, as well as test results, pending tests, and follow-up appointments [32, 60, 72]. ADA recommends that all patients with inpatient hyperglycemia have a scheduled outpatient follow-up visit with either their primary care provider, endocrinologist, or diabetes care and education specialist within 1 month of discharge. This appointment (in-person or telehealth) should be sooner (within 1–2 weeks) if diabetes medications are changed or if glucose control was not achieved prior to discharge [33, 34, 60, 73]. The specifics of the appointment should include appointment date, time, location, phone number, and provider name [32]. Direct referrals for outpatient diabetes services increase the chances of patient follow-up [74]. Knecht et al. reported that only 20% of discharge notes had a plan for outpatient diabetes follow-up [71]. Proper handoff needs to occur with the outpatient primary care provider to prevent gaps in care or adverse events [60]. Discharge documents should also include blood glucose targets and frequency as well as definitions and treatment for hyper- and hypoglycemia [32, 72].

Patient Education

Chapter 29 discusses in more detail inpatient diabetes education; the purpose of this section is to address strategies to overcome education barriers as it relates to hospital discharge. An education needs assessment is vital to understand and to address relevant barriers as early in the hospital stay as possible. The patient should be updated throughout their hospital stay regarding the anticipated discharge plan as opposed to only on the day of discharge [47]. Improved HbA1c and lower risk of readmission have been reported due to inpatient diabetes education, including education by dedicated diabetes educators or by pharmacists [75–78]. Other studies have shown improved medication adherence and diabetes knowledge at 3 months from inpatient survival skills education [79]. Earlier education in the hospital stay was a significant predictor of reduction in HbA1c [76]. In terms of who performs the inpatient education, different models exist depending on institutional need including a dedicated diabetes educator as part of or independent of a multidisciplinary endocrine service, a diabetes-specialty mid-level provider, and a decentralized approach utilizing bedside nurses, dieticians, pharmacists, and other team members, or by general hospital staff [80].

Implementation of an interdisciplinary diabetes champion program can help assess patient education needs, start diabetes education early in the admission, and escalate when necessary to a CDCES; it has even been reported to reduce inpatient and discharge insulin errors [81]. Utilizing registered dieticians inpatient can reduce healthcare costs by shortening length of stay [82]. While both AACE and ADA support the inpatient use of CDCES team members, only 24% of surveyed diabetes educators are working in an inpatient capacity [80, 83]. One of the challenges for dedicated inpatient diabetes educators is the lack of insurance reimbursement for services [80]. Additionally, if a hospital has one hired CDCES, it is not feasible for one individual to see every patient with diabetes. If a multidisciplinary approach is not available, then the physician and/or nursing staff should provide diabetes education [46]. Focusing on patients with DM with the greatest risk of readmission (e.g., comorbidity burden, insurance type, and insulin) should be a priority [11].

Teach-back method should be incorporated to help with patient retention and comprehension [12, 43]. Patients should also be able to repeat back who is their healthcare provider managing their diabetes outpatient as well as when they should contact them [60]. Patients need to play an active role in their diabetes management, and all decisions should be made together with the provider [46]. Content should be supplemented in print and/or video format; cartoons have even shown improved adherence for patients with low health literacy in other disease states [29, 79]. Health literacy-sensitive interventions can have a positive impact on HbA1c [84]. Survival skills that need to be taught during the inpatient stay include: blood glucose monitoring and glycemic goals, hyper- and hypoglycemia recognition and treatment, healthy food choices, antidiabetic regimen for discharge, sick day management, and proper use and disposal of needles/syringes [46, 60, 79, 80]. Joint Commission for Advanced Certification in Inpatient Diabetes Management specifies that newly diagnosed patients or those with identified deficits need the aforementioned skills taught prior to discharge [16]. For patients with limited or no English proficiency, a professional interpreter service (remote or in-person) can improve satisfaction and clinical outcomes [85].

Post-discharge Support

Patients with diabetes-related admissions or those new to insulin should receive visiting nurse services within 2 days of discharge [57]. Whitehouse et al. reported decreased rates of 90-day rehospitalization and HbA1c change for patients with diabetes who received inpatient diabetes self-management education (DSME) plus home care compared to DSME alone [86]. Another study combined one in-person home visit with weekly virtual DSME for 4 weeks after discharge; HbA1c improved by 1.1% at 3 months, and no patients were readmitted to the hospital [87]. There have been mixed results in the effectiveness of 48–72 h phone call follow-up independent of other TOC interventions [88].

There is abundant evidence to support various transitions of care models for patients with other chronic disease states. For example, the Transitional Care Model utilizes an advanced practice nurse (APN) as the primary coordinator starting within 24 h of hospital admission. The APN helps develop patient-centered care planning, provides inpatient education, communicates with the inpatient team and the primary care provider (PCP), and follows the patient for up to 2 months after discharge (via home visits and/or telephone support). This program was trialed in one patient with diabetes and could potentially be implemented on a larger scale [89].

Utilizing a CDCES nurse or nurse practitioner for outpatient telephone follow-up has had varying success depending on the model. In one study, inpatients with hyperglycemia were randomized to receive 3 weekly phone call interventions by a CDCES nurse starting 1 week after hospital discharge. There was no difference in readmission rates but a significant difference in patients attending follow-up appointments versus standard of care [90]. Inpatient diabetes education with a CDCES along with a transition program (telephone follow-up and contact with the PCP) was associated with a significant reduction in HbA1c; predictors of HbA1c reduction included higher baseline HbA1c, older age, initiation of insulin, and earlier education [76]. Brumm et al. reported improved HbA1c and 30-day readmission (though not statistically significant) after a transitions of care model was implemented for patients admitted with uncontrolled diabetes and psychosocial challenges [91]. The inpatient diabetes educator nurse practitioner (NP) provided inpatient education, handouts at a sixth-grade reading level, phone number to a 24/7 nurse hotline, weekly telephone interventions after discharge for 30 days, and a face-to-face visit post-discharge for some patients [91]. One randomized controlled trial studied an inpatient diabetes management and education workflow for patients admitted for reasons other than diabetes, which included inpatient endocrinology consults, inpatient education by a CDCES NP, diabetes discharge medication instructions, and written handoff with the PCP versus standard of care [92]. Results showed improvement in glycemic control for insulin-naïve patients 1 year after discharge; no significant difference was seen in patients already on insulin [92].

For high risk or newly diagnosed patients with diabetes, a CDCES transitions of care clinical pharmacist service improved HbA1c at 3 and 6 months and reduced 30-day all-cause readmissions. Services by the pharmacist included inpatient diabetes survival skill education (with handouts at a 5th–7th grade reading level) as well as post-hospital follow-up (at the primary care pharmacist clinic or telephone follow-up until seen by a PCP) [78]. Another transitions of care pharmacist study helped improve medication adherence (measured by prescription days covered), HbA1c, and follow-up rates [93]. One TOC pharmacist counseled patients on the Association of Diabetes Care and Education Specialists 7 (ADCES7) self-care behaviors (focusing on medication adherence). Additionally, all patients received a 30-day supply of discharge medications, and all patients were scheduled with their PCP and referred to the outpatient diabetes clinic [93].

An interprofessional transitions of care clinic for patients with diabetes was effective in decreasing 30-day readmission along with making clinically relevant medication changes in 64% of patients [73]. This service was provided by a clinical

pharmacist and provider (endocrinologist or endocrinology NP) within 1–2 weeks of hospital discharge [73]. For patients admitted with diabetes-related problems, a transitions of care clinic within 2–5 days of discharge was also proven to be effective for indigent or Medicaid patients without a PCP (though the benefit was not seen for patients originally admitted for non-diabetes problems) [94]. Patients with new diabetes regimens or significant changes to previous regimens may benefit the most from very close follow-up [32, 94].

Technology is also being utilized to help with transitions of care for patients with diabetes. National organizations like ADA have virtual education options, which may be helpful especially in locations that lack outpatient appointments with a CDCES (e.g., ADA's Living with Type 2 Diabetes program) [34]. Lyu et al. reported improvements in glycemic control and quality of life utilizing a 3-month web-based transitional care program after hospital discharge [95]. This web program consisted of patient-specific disease self-management, health education (six 20-min classes), group interaction, remote counseling, and daily data collection with reminder messages if not recorded (diet, exercise, blood glucose, and medication use) [95]. Zhang et al. are currently recruiting patients to a multicenter randomized control trial studying a mobile health-based transitional care intervention for patients with type 2 diabetes [96]. The app contains patient health records, medications, electronic diary (e.g., patients can record BG values), remote monitoring by a clinical nurse, outpatient appointments, diabetes education material, and remote consultation with the transitions team [96].

Future Directions

As our world and healthcare delivery continues to grow and change, it is important to consider future potential and innovative ideas to improve patient outcomes, specifically in relation to diabetes. While many other industries around the world have transitioned to web or app-based services to communicate with clients, healthcare has lagged, which can affect a patient's ability to communicate with their healthcare team. Mobile health-based transitional care interventions have the potential to improve transition home and communication with patients after discharge [95, 96]. Applying continuous glucose monitors prior to discharge or using internet-based glucometers should also be studied in conjunction with remote monitoring and a transitions of care clinic or virtual DSME programs [87, 97, 98]. Improved communication after discharge along with remote monitoring can potentially help patients and healthcare providers bridge the gap between inpatient and outpatient settings.

Electronic health records should be leveraged to highlight high-risk patients with diabetes and to help coordinate transitions of care (e.g., transition of care or discharge summary tab). Diabetes discharge checklists should be incorporated into the EHR to help prevent unintended errors or omissions by reminding prescribers and team members of what needs to be done prior to discharge [34]. Implementing

inpatient social determinants of health (SDOH) screening tools and appropriate interventions and referrals could help improve patient outcomes [99]. Finally, standardizing and increasing the use of dedicated team members or teams to help coordinate discharge, education, and follow-up for patients—such as patient care navigators, discharge nurses, pharmacists, certified diabetes care and education specialists, and/or case managers—could also improve transitions of care [34, 76, 78, 91–93, 100].

Conclusion

In order to effectively and safely transition patients with diabetes home from the hospital, multiple strategies need to be employed and multidisciplinary communication is vital. Discharge planning and identification of barriers needs to occur shortly after admission. A workflow should establish who educates the patient and what is taught inpatient (e.g., survival skills, ADCES7), along with utilizing both teach back and written handouts in the patient's respective language. Post-discharge support should include: detailed discharge documents, medication reconciliation, follow-up appointments, follow-through with the pharmacy, and contact information for medical personnel in the event of side effects, hypoglycemia, or hyperglycemia. Lastly, if hospitals have the resources, implementing a previously published transitions of care program can help reduce readmissions and improve blood glucose.

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Appendix: Inpatient Diabetes Management Guide

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Please use this inpatient diabetes management guide as a quick reference tool. It reflects the practice patterns at our institution and was designed for use by the primary care teams to help streamline diabetes care. As you have read throughout the book, there are sometimes several methods for management in various clinical scenarios. Please refer to the individual chapters for in-depth discussion and mention of all the variety of techniques for inpatient diabetes practice, as well as the supporting evidence base.

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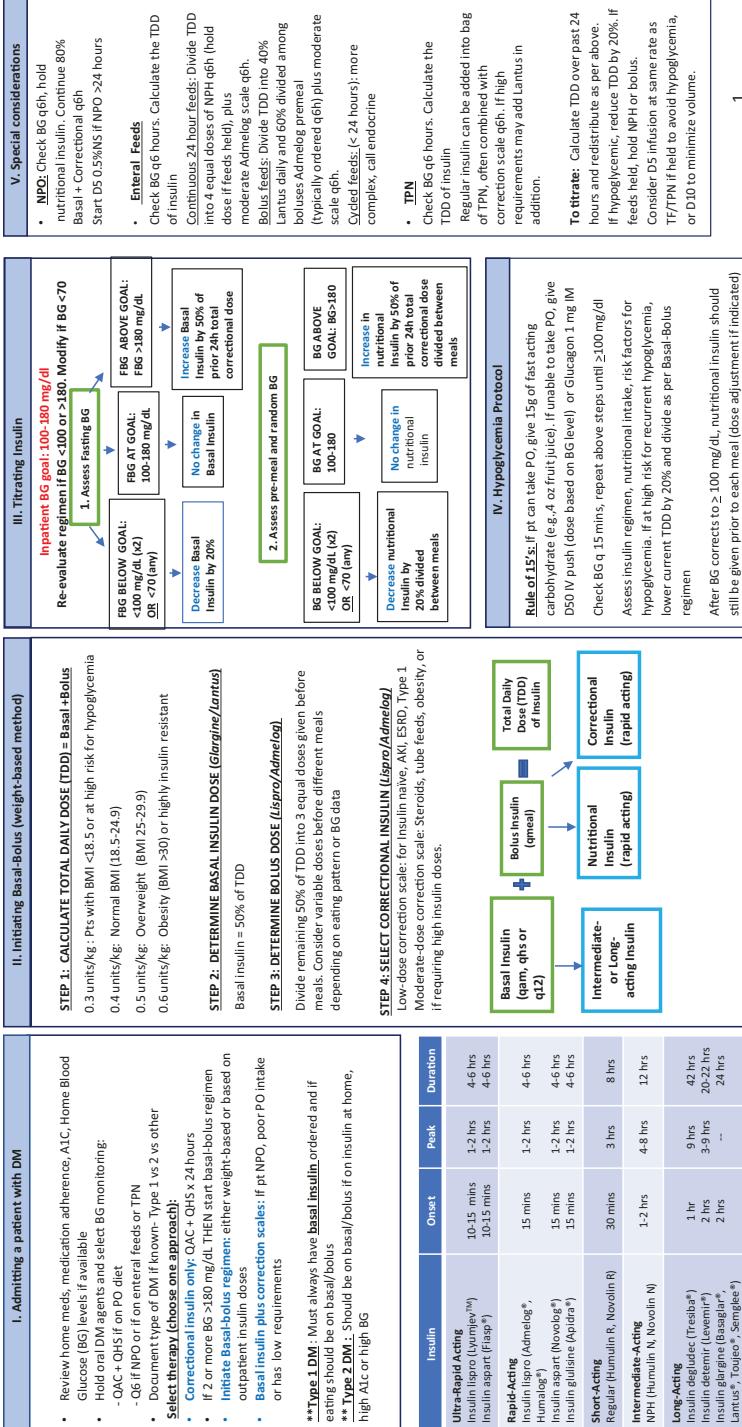
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Inpatient Diabetes Management Guide



Inpatient Diabetes Management Guide

| Glucocorticoid therapy | | Managing Mild DKA in non-ICU setting | | Coding tips | |
|--|--|---|---|--|---|
| <ul style="list-style-type: none"> In non-DM pts, monitor BG x 18 hrs and if 2 or more BG levels >280 mg/dL, initiate basal/bolus Calculate TDD-Give 40% as Basal & 60% as bolus <ul style="list-style-type: none"> Anticipate post-prandial hyperglycemia by increasing the nutritional insulin doses Titrate insulin doses as steroids are adjusted In general, % of insulin change should be half the % of steroid dose change | | <ul style="list-style-type: none"> Differentials: starvation ketosis or other causes of metabolic acidosis (lactic, acidosis) Check if patient has received SGLT2i within past 3 days Give STAT dose of Lantus if not already given. Can use 0.2 units/kg or home dose etc. If Lantus was already given earlier, consider dose of NPH for extra basal insulin. Correction scale q 4h: FS < 4h NPO/IV fluids Trend DKA labs: t BHP/CMP BHP, VBG Once anion gap normalized then resume PO, mealtime insulin | SGLT2 inhibitors Canagliflozin (Invokana) Dapagliflozin (Farxiga) Empagliflozin (Jardiance) Ertugliflozin (Stegliro) | Newer agents Sitagliptin (Januvia) Sasagliptin (Onglyza) Linagliptin (Tradjenta) | GLP1 Agonists Dulaglutide (Trulicity) Irraglutide (Victoza) Exenatide (Bydureon, Byetta) Semaglutide (Ozempic) |
| <ul style="list-style-type: none"> Obtain Endocrinology consult Criteria to continue pump iplt: Pump functioning, pt capable of self-management (A&D), pt agreeable to self-manage, not critically ill, not in DKA, has enough pump supplies (site change q 3 days) Criteria to dc pump iplt: examples: AMS, DKA, severe hyperglycemia, hypoglycemia, pump malfunction, no pump supplies If pts are transitioned from pump to subcut insulin, pump should be discontinued 2h after the first dose of basal insulin Administration of basal insulin is especially important in patients with type 1 DM who always need insulin on board to prevent DKA | | Pts on pre-existing insulin pump Seen with SGLT2i class Diagnosis BG > 250, Bicarb<18, pH<7.3, ketosis, BHb > 3 mmol/L Treatment: IVF with LR preferred for initial Mx. Replete lye especially K If mild may be managed outside ICU (see above section) IV Insulin, Administer D5 with IV insulin to maintain euglycemia Transition from IV Insulin to Basal/Bolus Once ketosis resolves and gap closes | Discharge planning • Begin dc planning on admission especially if pt will require new outpatient insulin use • Consider insulin regimen if A1C > 9 - Basal plus oral vs Basal/bolus • While converting from iplt: Basal/Bolus regimen or DPP4i/mixed insulin for dc - convert unit-per-unit or reduce dose by 20% • Give mixed insulin twice daily 2/3 prebreakfast and 1/3 before dinner • Consider de-escalating DM treatment in elderly if A1C > 8.0 (-7.8%) • Insulin teaching for pts and/or families for pts new to insulin • Check coverage & authorization needs: for new agents – many insurance require patients be on metformin (or proven contraindication/in intolerance) w/ or w/o prior authorization • Nutritional consult & diabetes education • Prescribe insulin pens with pen needles, test strips, alcohol swabs, glucose tablets, and glucagon kit in the discharge prescription if needed • For appointment with MD or Endo especially for pts on insulin and/or with A1C > 9 • Document post dc app in chart – time & date | Use of Linglifitin for Inpatient use: **NEW** • New society recommendations proposing use of DPP4i inpatient for mild hyperglycemia • Linglifitin 5mg po daily Critera for use: • HbA1c < 7.5% • BG = 180-200 mg/dL • If on home insulin: 0.6 units/kg/d • May be used with correction scale or with basal insulin and correction scale • If glucose remains > 200 with DPP4i alone/correct then add basal insulin. • If on basal insulin + correction scale + DPP4i and still with ongoing hyperglycemia recommend stop DPP4i and change to basal/bolus insulin plan. • Avoid DPP4i with history of pancreatitis, pancreatic cancer, biliary disease. | Discharge Planning: Non-Insulin Agents for CKD Metformin Glyburide, Glipizide, Glimepiride Alogliptin (Nesina) |
| <ul style="list-style-type: none"> Target BG in perioperative period is 140-180 mg/dl If pt NPO, decrease Basal insulin to 80%, hold mealtime insulin SGLT2 inhibitors must be d/cd 3-4 days prior to Sx due to risk of euglycemic DKA while NPO <ul style="list-style-type: none"> Canagliflozin, Dapagliflozin, Empagliflozin, Ertugliflozin & Naegarginide (Saxagliptin Onglyza) If inadvertently taken check DKA labs. Metformin held on day of surgery | | Perioperative No restriction | Pearls • Pt with Type 1 DM will ALWAYS need exogenous basal insulin even if NPO or else will lead to DKA • Avoid hyperglycemia with BG > 250 for >48 hrs | Perioperative Reduce dose to 50mg for eGFR 30-<45 mL/min Administer post dialysis in HD pts | Perioperative Reduce dose to 25mg for eGFR <30 mL/min Administer post dialysis in HD pts |
| <ul style="list-style-type: none"> Target BG in perioperative period is 140-180 mg/dl If pt NPO, decrease Basal insulin to 80%, hold mealtime insulin SGLT2 inhibitors must be d/cd 3-4 days prior to Sx due to risk of euglycemic DKA while NPO <ul style="list-style-type: none"> Canagliflozin, Dapagliflozin, Empagliflozin, Ertugliflozin & Naegarginide (Saxagliptin Onglyza) If inadvertently taken check DKA labs. Metformin held on day of surgery | | Perioperative No restriction | Pearls • Pt with Type 1 DM will ALWAYS need exogenous basal insulin even if NPO or else will lead to DKA • Avoid hyperglycemia with BG > 250 for >48 hrs | Perioperative Reduce dose to 50mg for eGFR 30-<45 mL/min Administer post dialysis in HD pts | Perioperative Reduce dose to 25mg for eGFR <30 mL/min Administer post dialysis in HD pts |

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