separately, making them a less preferred choice in patients with T1DM. Despite this major limitation, premixed insulin given twice daily before breakfast and before dinner along with a short acting insulin administered before lunch is a reasonable option in a large number of patients with T1DM. This is especially relevant in a resource poor country like India, as a well as a needle phobic society. This regimen brings down the prick count from 4 to 3 per day (compared to basal-bolus regimen) and also results in better compliance and significant reduction in treatment costs. It is a good practice to resuspend the premixed insulin preparation by gently shaking or rolling the pen or vial before injection.

3. Intensive insulin regimens

These regimens aim to replicate normal insulin secretion by providing separate basal and prandial insulin doses, and are now recommended in all age groups, even young children with T1DM. Patient education and motivation is essential for their success.

a) Basal bolus regimen: multiple daily insulin injections (MDII)

Here basal insulin (intermediate-acting or long-acting analogs) is injected once or twice a day and short-acting insulin (regular or rapid-acting analogs) is given before each major meal (and whenever a large snack is eaten). Nearly 40-60% of TDD is given as the basal analog (preferable if patient can afford) or as intermediate- acting NPH insulin. The remaining dose is given as multiple boluses of regular insulin or rapid-acting insulin analog in 3-4 or greater number of divided doses. The dose of basal insulin is adjusted depending upon the fasting glucose while the bolus doses are adjusted by levels of post-meal glucose and postprandial glucose excursion. The control achieved with this regimen is close to that with continuous subcutaneous insulin infusion (CSII) and there is considerable flexibility in the timing and quantity of meals and exercise[9,10]. However, the frequency of severe nocturnal hypoglycemia may be higher than CSII. The expenses involved in MDII are considerably lower than for CSII. With patient/family education and motivation, it can be successfully used in smaller towns and even in rural areas, where lesser resources are available and technical back-up required for CSII is not available.

b) Continuous subcutaneous insulin infusion (CSII)

This topic will be discussed only in brief. CSII provides the most physiological insulin replacement for patients with T1DM, especially when it is combined with CGMS input. It has been recommended for all age groups, including children[11], but should only be used if the patient and family is motivated, willing to test glucose frequently by finger-prick or CGMS, and if adequate resources are available. Studies and meta-analyses suggest that it provides slightly improved glycemic control and, importantly, a reduced frequency of severe nocturnal hypoglycemia[9,10,12] compared with MSI. A Cochrane review suggests that CSII provides improved HbA1c when compared with MSII [-0.3% (-0.1-0.5%)] in children and in adults with T1DM[10].

Careful selection of patients, constant education and regular monitoring are essential for the success of pump therapy. Unless the patient and family are motivated and agree to monitor capillary glucose 4-6 times per day by finger prick or by CGMS, and to adjust insulin doses by giving appropriate boluses, glycemic control is unlikely to improve on CSII. Patients who may be selected for CSII include those with brittle diabetes, recurrent hypoglycemia and/or hypoglycemic unawareness, persistent fasting hyperglycemia due to “dawn phenomenon”, women planning pregnancy or pregnant women with type 1

DM (to intensify glycemic control) and children/adolescents who desire greater flexibility in their lifestyle while being on insulin therapy. The costs of CSII should be discussed with the patient and family since it considerably greater than MSII, especially if used along with CGMS. In addition, technical resources for CGMS are not available in many cities in India and there is a paucity of pediatricians or physicians who are familiar with CSII use.

All insulin pumps currently use rapid-acting insulin analogs. Insulin is delivered continuously at a basal rate throughout 24 hours, though the rate is changed at different times. Higher doses are required in early morning after 4 AM (due to insulin resistance caused by release of counter regulatory hormones), while lower doses are required earlier at night, during the day, and at times of exercise. Insulin boluses are given before each meal and snack (meal bolus) in quantities which are decided by the patient or care-giver depending upon the pre-meal glucose level, carbohydrate content of the meal, and exercise being considered.

In general, pumps to deliver CSII may be either "open-loop" or "closed-loop". In the former, insulin is infused at variable basal and bolus rates which are set by the user. Glucose is measured separately either using multiple finger pricks or using CGMS, and rates of bolus insulin are decided by the patient using various "bolus calculators" which may be incorporated into the pump or available separately. Newer pumps can use information received from CGMS to automatically suspend insulin infusion for a short time period once the glucose has a decreasing trend or approaches hypoglycemic levels. More recently, "hybrid closed loop" insulin pumps are available, which utilize the glucose values available through CGMS to automatically increase or decrease basal insulin delivery rates. However, the bolus insulin dose is still decided by the patient. Recent studies suggest that their use may results in lower frequency of hypoglycemic episodes[13].

The risks associated with use of CSII per se are diabetic ketoacidosis (DKA) and catheter site infection/contact dermatitis. It should be remembered that DKA may occur rapidly in setting of interruption of insulin supply due to technical failure in CSII, since the action of rapid acting insulin used in the pump lasts for only few hours. It is therefore recommended that a patient using CSII should have back-up insulin for subcutaneous injection in case of pump malfunction.

Insulin dose adjustments

Insulin dose adjustments should be performed to achieve target blood glucose and HbAIc levels. Adjustments should be made based on daily pattern of blood glucose levels, food consumption and exercise (see chapter on "Monitoring of metabolic control"). Adjustment of doses should be carefully done during exercise and sick days. During the times of acute illness, in addition to other aspects of therapy (increased fluids, frequent monitoring of blood glucose, testing urine ketones), increased regular or rapid-acting insulin (5-10% of TDD) at 4-6 hourly intervals is often required, in addition to the daily insulin dose (also see "Sick Day Guidelines" in on "Education").

Insulin-carbohydrate ratio (ICR) and insulin sensitivity factor (correction factor):

The carbohydrate content of meal is the major dietary component which will produce rapid elevation in blood glucose. Hence, the insulin dose has to be adjusted to deal

with differing amounts of carbohydrate intake in a meal. The approximate amount of carbohydrate which will be covered or disposed of by 1 unit of short acting insulin (ICR) can be calculated as: 450 or 500 divided by TDD for regular insulin or rapid acting insulin analogs, respectively. In addition to carbohydrates, fat and protein content of the meal also affect late post-prandial glucose levels, though to a lesser extent. Insulin sensitivity factor, defined as amount of blood glucose reduction (mg/dl) expected with 1 unit of short acting insulin, is calculated as: 1500 or 1800 divided by TDD for regular insulin or rapid- acing insulin analogs, respectively. The glucose level above the desired pre- meal glucose level is calculated (ambient blood glucose-desired pre-meal blood glucose) and divided by the insulin sensitivity factor to derive the supplemental (or correctional) insulin required.

Summary

All children and adults with T1DM require insulin as soon as they are diagnosed and continuously thereafter throughout life. Insulin therapy has constantly evolved over the last 100 years. While insulin analogs provide increased flexibility and probably a reduced risk of hypoglycemia, their use is associated with significantly increased treatment costs. The usage of these agents should therefore be individualized to settings where there is a distinct advantage associated with their use such as in toddlers with fussy eating patterns, school or college going children and teenagers with limited recess times, and patients with nocturnal or delayed hypoglycemia on conventional insulin preparations. Physiological insulin regimens, either MDII or CSII, should be used as far as feasible in all age groups, including young children. CSII provides the most physiological insulin delivery, but it its use in Indian setting is limited by cost, technical expertise and healthcare provider awareness. The level of motivation and education and financial resources available with the patient and family should be taken into account when deciding which insulin and regimen to use.

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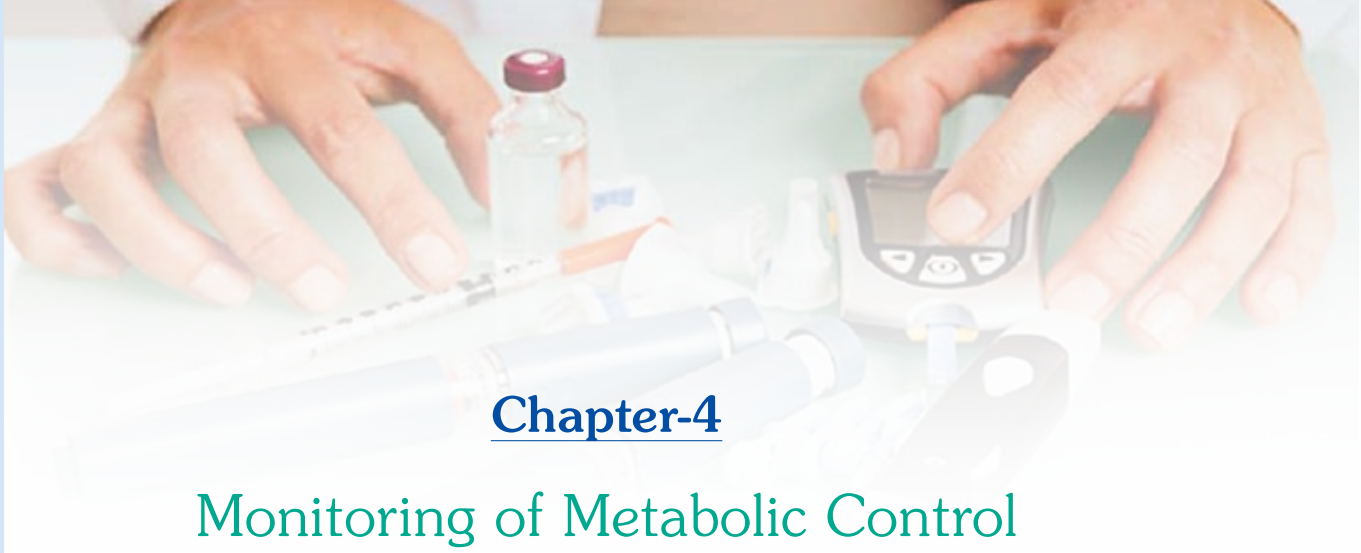

Chapter-4

Monitoring of Metabolic Control

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Introduction

Blood glucose monitoring is a key factor that predicts glycemic control in patients with type 1 diabetes mellitus (T1DM). Diabetes Control and Complications Trial (DCCT) trial provides evidence that achieving good glycemic control in the initial years of T1DM results in reduced incidence of macrovascular and microvascular complications. This foregrounds the importance of achieving near-normal glycemic status, especially during the early years. This chapter highlights the various aspects of monitoring in patients with T1DM.

Self-monitoring of blood glucose (SMBG)

Glycemic control for patients with T1DM of any age should be assessed based on frequent SMBG. SMBG is an intrinsic part of intensive therapy in T1DM. The rewards of SMBG are manifold: a) it helps to supervise immediate and daily blood glucose control, b) it aids to ascertain immediate and daily insulin requirements, c) it guides insulin adjustments to decrease fluctuations in blood glucose levels, and d) it facilitates timely management of hypoglycemia and hyperglycemia. SMBG not only allows modulation of doses and timing of insulin, but also timing and content of meals and snacks based on blood glucose results. It is also important for patients with T1DM not managed with intensive insulin therapy, although, such patients may require somewhat less frequent testing[1,2].

The American Diabetes Association (ADA) recommends that patients with T1DM should monitor capillary blood glucose prior to meals and snacks, at bedtime, occasionally postprandial, prior to exercise, when they suspect low plasma glucose, after treating low plasma glucose (till blood glucose is normal), and before starting any critical tasks such as driving[3]. In addition, blood glucose should be checked intermittently (every 1-2 weeks) at 1-3 am for nocturnal hypoglycemia, and frequently during intercurrent illness and travel. SMBG helps to identify hypoglycemia much before the appearance of symptoms, thereby avoiding overcorrection-related hyperglycemia. SMBG enables patient (and physician) to understand the response to treatment, and make appropriate treatment decisions.

Frequent SMBG has been demonstrated to improve glycemic control, and to reduce the absolute frequency of severe hypoglycemic episodes in children[4-6]. It is important to remember that frequent SMBG may translate into improved glycemic control only when these values are used in a systematic manner (by patient and physician) for making decisions on insulin dose adjustments, and/or meal/snack timing and content. Zieger et

al. found that the frequency of SMBG is highest in children under the age of six years, which decreases as the child grows older[4]. The predictors of lower frequency of SMBG include low self-esteem, higher levels of stress, and inadequate parental support. The presence of psychosocial support and parental supervision has been found to improve the frequency of SMBG in older children.

Equipment

A wide variety of glucometers are available in the market for SMBG testing. The use of a glucometer does not require much technical expertise and can be used easily by adults as well as children. Impedance-based glucometers are considered to be more accurate compared to colorimetric-based glucometers. Most glucometers utilise one of the three enzymatic reactions-glucose oxidase, hexokinase and glucose dehydrogenase. Glucose dehydrogenase may give false positive readings with non-glucose sugars present in pharmaceutical preparations such as peritoneal dialysis solution (icodextrin) and intravenous immunoglobulin[7,8]. Such erroneous readings may result in potentially fatal dose calculation errors.

Accuracy of glucometers

Although glucometers analyze glucose in whole blood, many meters provide a plasma equivalent value using a built in algorithm (to convert whole blood glucose to plasma glucose). Their readings are most accurate when blood glucose ranges from 60-160 mg/dl. For blood glucose values both above and below this range, larger deviations from venous blood glucose values have been observed. Additionally, SMBG values approximate the venous glucose values better in the fasting state; in the postprandial state, the capillary values may be higher by around 10-20%. It is advisable to cross-check SMBG values with venous plasma glucose values, when in doubt. ADA has recommended an intermediate goal of limiting error (for 95% of glucometer values) to < 15% at glucose concentrations ≥ 100 mg/dl and < 15 mg/dl at glucose concentrations < 100 mg/dl[9].

Coded versus non-coded meters

There may be a lot-to-lot variation in the amount of enzymes in blood glucose strips, resulting in variation in amount of electric current produced per unit of glucose[10]. To minimize this variation, a code is provided that calibrates the meter for that batch of strips. However, miscoding errors are frequent, and about 16% patients miscode, leading to errors as high as 30%. This may result in incorrect insulin dosing, and hypo or hyperglycemia. With improved enzyme purification methods, and better quality control, the blood glucose strip standard variation has reduced dramatically. This has resulted in decline in availability of coded meters and emergence of non-coded meters, which are accurate and patient- friendly.

Control Solution (CS)

CS contains a known amount of glucose, and when applied to the test strip it aids in assessing the working status of glucometer. Although the usage of CS is clearly stated to improve accuracy of SMBG, storage and prevention of decline of glucose in the solution is itself an issue of concern[11,12]. Additionally, it is not readily available for all glucometers.

Analytical and pre-analytical variables

Analytical variables (intrinsic to glucometer and glucose strips) and pre-analytical variables (related to patients) could affect accuracy of SMBG. Briefly, the common causes for inaccurate readings by glucometer include use of expired tests strips, improper condition of strip storage (extremes of temperature or humidity), unwashed hands, and low or high hematocrit and hypotension. Blood volume required for glucometers is as low as 0.3 µl[13]. For the visually impaired, size of the screen and font sizes need to be adjusted. The option of using a talking meter that provides verbal guidance on the process is also available. Dexterity is another important issue that needs to be considered in patients advised SMBG.

Reducing pain with SMBG testing

Pain with SMBG may be reduced by rotating fingers, using side of fingers rather than the central fat pad, using fresh lancet for each prick, using lancet with depth gauge and adjusting it to a minimal setting which gives an adequate blood drop, using smaller gauge lancet and using alternate sites for testing (discussed in next section).

Sites for testing

Alternate testing sites have been advised for minimising pain associated with lancing for blood drop. These include the palm of the hand, the forearm and the thigh. Compared to the fingertip, the density of pain receptors at these sites is much lower, resulting in reduced pain with testing. Fineberg et al. demonstrated that alternative site testing (using arm) provides accurate results, while being less painful compared to the finger prick testing[14]. In the fasting state, glucose readings from alternative sites are nearly similar to the fingertip. However, these sites should not be relied upon at times when blood glucose is expected to change rapidly (such as after meals, insulin and exercise). Additionally, hypoglycemia identification is difficult, and these sites should also not be used at the time of suspected hypoglycemia.

Timings of SMBG

Both pre-meal and post-meal (2 hours after beginning of the meal) blood glucose values should be monitored, however, their significance may vary from one patient to another. Individuals with HbA1c of less than 8-8.5% need to check their postprandial glucose levels more often, since these contribute disproportionately to the dysglycaemia. On the other hand, patients having HbA1c above this threshold should concentrate on normalizing the fasting and pre-prandial values before attempting control of postprandial hyperglycemia[15,16]. Blood glucose should be checked whenever hypoglycemia is suspected, and with re-evaluation after correcting the hypoglycemia (till the time normal blood glucose level is achieved). Additionally, monitoring of blood glucose at 1-3 am (for nocturnal hypoglycemia), before and during exercise, before performing critical tasks (such as driving), frequently during an intercurrent illness and travel is important.

Targets for SMBG

The blood glucose targets recommended (Table I) by International Society of Pediatric and Adolescent Diabetes (ISPAD) are: pre-meal: 70-130 mg/dl, post- meal: 90-180 mg/dl and pre-bed: 80-140 mg/dl[17].

Table I: Blood glucose targets in children and adolescents with T1DM according to various professional bodies

	ISPAD [17]	NICE [18]	ADA [19]
Pre-prandial (mg/dl)	70-130	70-126	90-130
Post-prandial (mg/dl)	90-180	90-162	-
Pre-bed (mg/dl)	80-140	70-126	90-150

ADA: American Diabetes Association, ISPAD: International Society for Pediatric and Adolescent Diabetes, NICE: National Institute of Clinical Excellence, T1DM: Type 1 Diabetes Mellitus

National Institute of Clinical Excellence (NICE) recommends pre-meal, post-meal and pre-bed blood glucose targets of 70-126 mg/dl, 90-162 mg/dl and 70-126 mg/dl respectively, while ADA recommends pre-meal and pre-bed blood glucose targets of 90-130 mg/dl and 90-150 mg/dl respectively[18,19]. However, it should be remembered that these blood glucose targets need to be individualised, and less stringent targets may be suitable for certain group of individuals (such as those with recurrent hypoglycemias, hypoglycemia unawareness and other comorbidities).

Maintaining and interpreting a blood glucose log

The frequency of SMBG may vary from 4-6 times per day in young children, especially the ones with poor glycemic control. A more liberal SMBG of 2-3 times per day may be advocated in children with a better glycemic control. Patterns, as opposed to intermittent problems, are best identified if there are a relatively large number of measurements every day. However, due to the substantial financial burden associated with regular 7-point blood glucose charting, less frequent glucose charting, with rotation of timings of blood glucose charting should be provided as an alternative option, especially in stable patients with T1DM[20]. In a subgroup of patients, cost constraints may hamper monitoring of even 1-2 blood glucose readings. In such a scenario, the Indian Society of Pediatric and Adolescent Endocrinology (ISPAE) recommends that testing could be reserved for sick days and episodes of hypoglycemia, and a "bare minimum" testing of 2 to 4 times per day for 2 to 3 consecutive days in a month could be used to evaluate blood glucose patterns[21]. In a setting where patient cannot even afford to perform the "bare minimum" testing, one may have to rely upon monitoring using urine glucose strips. The colour obtained on the urine strip should be indicated against the time of performing test on a standard blood glucose monitoring chart. For an illiterate patient who may have difficulty in writing the colour name, coloured pencils could be provided to indicate the appropriate colour. Urine glucose will be positive only if blood glucose is more than 180-200 mg/dl, and it will not be able to detect hypoglycemia. It should be remembered that urine glucose provides an extremely crude method of evaluating glycemic control that should only be used as a last resort in patients with significant financial constraints.

The documented SMBG readings should be reviewed during each hospital visit. Apart from blood glucose readings, the log should contain a column for remarks and insulin dose injected on a given day. The remarks should address the possible reasons for aberrant glucose values-both hyperglycemia (such as eating outside, less dose of insulin injected, lack of physical activity, fever) and hypoglycemia (such as delayed meal timings, decreased food intake, vomiting, excessive exercise, increased dose of insulin injected). It is also important to correlate SMBG log with HbA1c values. A lack of correlation between

the two may be indicative of faulty glucometer/strips, incorrect documentation by the patient and/or family members, or presence of factors decreasing the utility of HbA1c as a marker of glycemic control (such as iron deficiency anemia, hemoglobinopathy, hemolysis). Many patients check blood glucose using a glucometer, but fail to enter these values in SMBG log or only enter values which are near-normal. It is important to counsel such patients on importance of SMBG documentation in achieving good glycemic control.

Apart from logbooks, today's technology offers other options such as use of downloadable software available with the meter that displays the data in a usable format. Some smart phone apps are available to enter glucose readings and other useful diabetes information (such as food intake and exercise). These include- mySugar (iPhone and Android), Glucose Buddy (iPhone and Android), On Track Diabetes (Android), and Glucool Diabetes (Android). Patients and/or caregivers can also be trained to look for patterns and also be encouraged to make minor alterations in their insulin dosage accordingly.

Patient education strategies are crucial in assuring successful management of SMBG feedback. The frequency of SMBG testing often decreases over time, because patients do not know how to respond to a high value, and may perceive that the treating doctor is more interested in HbA1c values than glucose logs[22]. In a study, the use of SMBG was successful in reducing A1C values when accompanied by training of patients and clinicians to collect and interpret SMBG profiles[23].

Insulin algorithms

Once a basic regimen of eating, exercise, and insulin dosing has been established, there could still be a day-to-day variability in blood glucose values. This may be effectively treated using an insulin algorithm in which the pre-meal dose of short-acting insulin is adjusted according to the blood glucose value and, for patients who use carbohydrate counting, anticipated carbohydrate content of the meal. Any changes in exercise can also be included in this calculation. The adjustments should be small in patients who are very sensitive to insulin or who are taking low doses of insulin (as with a subcutaneous continuous insulin infusion via a pump).

Monitoring and interpretation of urine and blood ketones

Urine ketones

Strips and tablets may be used for quick monitoring of urine ketones at the bedside. Nitroprusside test is commonly used for ketonuria; however, it can only estimate acetone and acetoacetate, and not beta-hydroxybutyrate. Presence of ketonuria in association with hyperglycemia serves a clue for metabolic decompensation. IDF recommends that in limited care settings, urine ketone test strips should be available and testing performed during illness with fever and/or vomiting, persistent polyuria with elevated blood glucose (more than 250 mg/dl), especially with abdominal pain or rapid breathing. Urine ketones may also be elevated in patients with T1DM as a physiological metabolic response to low carbohydrate diet (e.g. Atkins diet), during pregnancy, following prolonged exercise, and in those with alcohol intoxication. False positive ketonuria may be encountered in those using drugs like penicillamine, captopril and mesna. False negative ketonuria is rarely encountered in patients with DKA and shock, as liver is the site of conversion of ketones to beta-hydroxybutyrate[24].

Blood ketones

The ratio of beta-hydroxybutyrate to acetoacetate, which is approximately 1:1 in normal subjects, can soar to as high as 10:1 in DKA[25,26]. Therefore, in ketosis, it is preferable to measure beta-hydroxybutyrate directly, whenever feasible. This can be accomplished either in the laboratory or by using the point-of-care ketone meters[27,28]. Home blood ketone monitoring is now possible with some glucometers (such as Abbott Freestyle), where the ketone strip is used (in a way similar to blood glucose strip) to provide blood ketone (beta-hydroxybutyrate) value (in mmol/L). Blood ketones should be always be interpreted along with concurrent blood glucose values. Blood ketones level <0.6mmol/L is considered normal. A level between 0.6 and 1.5 mmol/L indicates mild elevation. In such a scenario, increased fluid and carbohydrate intake should be advised if blood glucose is less than 180 mg/dl, while if blood glucose is more than 180 mg/dl, additional dose of insulin may be required. If the ketone levels are between 1.5 and 3 mmol/L, there is a high risk for ketosis. Such patients need more fluids and additional dose of rapid acting insulin immediately. Blood ketone level more than 3 mmol/L is usually associated with acidosis, and warrants emergency admission and management for DKA.

It is important that patients with T1DM keep blood ketone (or urine ketone) strips at home for use during a sick day, and periodically check that these are not beyond the expiry date.

HbA1c and other glycated products

HbA1c measurement should be performed at least every 3 monthly in patients with T1DM[17]. The measurement should be performed using an assay which is certified by National Glycohemoglobin Standardisation Program (NGSP), and standardised to the DCCT reference assay. For children and adolescents with T1DM, a HbA1C target of <7% is recommended by ISPAD, while NICE and ADA recommend a target of <6.5% and <7.5% respectively[17-19]. However, these targets need to be individualised, and each patient should be treated to achieve a value as close to normal as possible whilst avoiding severe hypoglycemia as well as minimising frequent mild to moderate hypoglycemia. The aim is to avert the long- term microvascular and macrovascular complications of diabetes, while also avoiding abnormalities associated with acute hypoglycemia and the associated neurological consequences.

Children below six years of age are at especially high risk of having adverse neurologic outcomes with severe hypoglycemia. Because they cannot self-identify hypoglycemia, caution need to be exercised in achieving target HbA1c in such individuals. In fact, many paediatric centres report that the average HbA1c is lowest in this age-group, reflecting the more complete caregiver involvement at younger ages. As teens advance towards adulthood, targets alike to those of the adult population should be approached, while recognizing that the hormonal alterations and psychological adjustments of adolescence make achieving these targets difficult. Of all age-groups, adolescents are currently the farthest from achieving HbA1c target of < 7.5%, reflecting the diabetes mismanagement that frequently accompanies the increased independence in diabetes care during the adolescent years, along with the effect of psychological and hormonal challenges of adolescence.

Hemoglobinopathies may interfere with HbA1c measurement due to the presence of haemoglobin variants [false high or low result with ion-exchange high-performance liquid

chromatography (HPLC)] or reduced red cell life span (false low result with any HbA1c method[29,30]. Certain hemoglobinopathies such as hemoglobin S (HbS), hemoglobin E (HbE) and β-thalassemia are relatively common in certain population groups in India[31,32]. While HbE is predominantly restricted to tribal population belonging to North-Eastern states, West Bengal, Odisha and Andaman and Nicobar Islands, the distribution of HbS is more extensive, being especially prevalent in central India. Similarly, the prevalence of β-thalassemia is known to be higher in Punjabis who have migrated from West Pakistan. The interference caused by a haemoglobin variant can be addressed by using alternative methods of HbA1c measurement, namely immunoassays (especially for HbE) and boronate affinity HPLC. On the other hand, for accelerated red cell turnover, an alternative non-HbA1c method of estimating intermediate to long-term average glycemic control such as fructosamine, glycated albumin and 1-5 anhydroglucitol should be relied upon. Among these, fructosamine is the most popular; it assesses the glycation of blood proteins such as albumin and reflects glycaemia over the past 2–4 weeks. Although useful in monitoring glucose control, these biomarkers are limited by cost, lack of availability and standardization[30].

Continuous glucose monitoring system (CGMS)

Subcutaneous glucose sensors that continuously measure interstitial fluid glucose levels (CGMS) are available, and approved for use in children. While SMBG provides a snapshot of glycemic data at a given point of time, CGMS provides comprehensive longitudinal data for a given day. CGMS can be of two types- retrospective (professional, masked) and real-time (personal, unmasked)[33]. The data from retrospective CGMS can be downloaded subsequently and reviewed in clinic while real-time CGMS allows real-time assessment of blood glucose fluctuations allowing remedial action to be taken by the patient or caregiver. The term “continuous” and “real-time” are relatively inaccurate since CGMS records glucose every 5 to 15 minutes (not continuous) and interstitial fluid glucose results lag behind blood glucose by approximately 7-15 minutes (not real-time). The CGMS sensor measures glucose in interstitial fluid based on the “glucose oxidase” enzymatic reaction. CGMS can be used alone (in patients on multiple subcutaneous insulin injection (MSII) or with continuous subcutaneous insulin infusion (CSII or insulin pump). Although the use of CGMS benefits patients using MSII and CSII both, the benefit is likely to be higher when used along with insulin pump (CSII), especially a sensor-augmented insulin pump.

CGMS is useful for optimizing glycemic control in motivated patients, and also for management of patients with a history of hypoglycemia unawareness. The improvement in glycemic control with use of CGMS has been shown to occur only in those patients who are committed to wear the device. Patient should be willing to use the device for at least 70% of the time. Therefore, like continuous subcutaneous insulin infusion (CSII) therapy, appropriate patient selection is very important. CGMS is useful for those with any of the following: hypoglycemia unawareness, more than 1 episode per year of severe hypoglycemia with no obviously preventable precipitating cause, frequent (more than 2 episodes a week) asymptomatic hypoglycemia, those with extreme fear of hypoglycemia, hyperglycemia (HbA1c level of 9% or more) that persists despite frequent testing, and pregnancy-associated hyperglycemia. CGMS is also helpful in assessment of glycemic variability, a parameter known to correlate with vascular complications, independent of HbA1c.

The procedure of CGMS sensor insertion is very simple, rapid and painless. The sensor, in the form of a membrane-clad, needle-shaped enzyme electrode, is inserted through the skin (usually upper abdomen) into the subcutaneous fatty tissue to have access to interstitial fluid. The device can be fixed, and usually remains in place for therapeutic monitoring for a period of seven days (varies from 3-14 days depending on the model). For most CGMS devices, the sensor needs to be calibrated with capillary blood glucose readings either four times a day (Medtronic iPro2) or two times a day (Medtronic Guardian Connect, Dexcom G4 Platinum, Dexcom G5 Mobile). The calibration should be done a time when blood glucose is expected to be relatively stable (fasting and pre-meals). Recently, a new CGMS sensor (Dexcom G6) which does not require calibration with capillary blood glucose values has been introduced in the market.

The real- time values can be readily accessed using a reader device and, a detailed assessment of the glucose variability can be analyzed by feeding the data to a computer. The alarm in the device (when using real-time CGMS along with an insulin pump or as a standalone device used along with a mobile app) helps in identifying and predicting low or high blood glucose levels based on the target level set.

The use of CGMS has been found to improve glycemic control, with higher time in target, and reduced number of hypoglycemic events. In the Juvenile Diabetes Research Foundation (JDRF) CGMS study, 322 children and adults with T1DM on intensive insulin therapy (predominantly CSII, 80% of the study participants) were randomly assigned to the use of CGMS or SMBGas a tool for blood glucose monitoring[34]. The primary outcome, change in HbA1c level over 26 weeks period, varied according to the age group (8-15 years versus 15-24 years versus ≥25 years). HbA1c change (0.53%, 95% CI: 0.35%-0.71%) was only found to be significant in adults aged ≥25 years, who also had significantly higher sensor use, compared to the participants belonging to the two other age groups. Similarly, in the DIAMOND study, the use of CGMS (versus SMBG) was associated with greater reduction in HbA1c (1% versus 0.4%, $p<0.001$) and lesser time spent in hypoglycemia (median time with glucose concentration <70 mg/dl: 80 minutes versus 43 minutes, $p=0.002$)[35]. In the HypoDe study, the use of real-time CGMS (n-75) was compared against conventional SMBG (n-74) in individuals with T1DM treated with MSII who had history of impaired hypoglycemic unawareness or severe hypoglycemia during the past one year[36]. The use of real-time CGMS was associated with a significant reduction in number of hypoglycemic events (mean number of events over 28 days reduced from 10.8 to 3.5 in real-time CGMS group versus reduction from 14.4 to 13.5 in SMBG group). Additionally, CGMS use has been found to be associated with decreased fear of hypoglycemia, lower diabetes-related distress and improved quality of life in various studies[37-40].

The lack of accuracy is an issue with CGMS sensors, especially when glucose concentrations are rapidly changing, ascribed to the retarded equilibration between the different physiologic compartments. Most CGMs are least accurate on day 1 of use (owing to the local inflammation) and when blood glucose in the hypoglycemic range[41,42]. Therefore, when taking a decision based on a CGM reading (such as taking extra insulin or else treatment for hypoglycemia), it is advisable to do a finger-prick blood glucose to confirm it. Nevertheless, the accuracy of CGM is acceptable in terms of clinical monitoring of patients with T1DM.

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Chapter-5

Acute complications-Diabetic Ketoacidosis, Hypoglycemia and Infections

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Section A - Diabetic ketoacidosis (DKA)

Epidemiology of DKA

Diabetic ketoacidosis (DKA) is a composite metabolic state of hyperglycemia, ketosis and acidosis occurring predominantly in the setting of severe uncontrolled diabetes. Euglycemic DKA, characterized by the presence of ketoacidosis in absence of hyperglycemia (blood glucose <250 mg/dl) has been reported in the setting of pregnancy, alcohol intake, reduced carbohydrate intake and treatment with sodium-glucose contransporter-2 (SGLT-2) inhibitors. DKA is the leading cause of morbidity and mortality in children with type 1 diabetes mellitus (T1DM), with a case fatality rate ranging from 0.15-0.30%[1-3]. In two pediatric intensive care unit (PICU)-based retrospective studies from India involving 68 and 55 children with DKA, mortality was reported at 12.7% and 13.2%, respectively[4,5]. Cerebral edema is the major contributor to morbidity and mortality in DKA. Due to the absence of adequate cerebral autoregulatory mechanisms and increased severity of presentation, young children are predisposed to this potentially fatal complication. Cerebral edema occurs in 0.5-1% of children with DKA and carries a mortality rate of 20-25%, accounting for about 60-90% of all DKA-related deaths in children[6-8]. According to data from developed countries, about 15-70% patients have DKA at the time of diagnosis of T1DM[9-14]. DKA at onset of diagnosis is especially common in children <5 years of age and in children with poor socioeconomic background. The prevalence of DKA at diagnosis was reported to be 28.7% among 2335 Indian youth with T1DM enrolled in the Registry of People with Diabetes with Youth Age at Onset in India (YDR)[15]. The risk of DKA in youth with T1DM varies from 1-15% per patient per year across various studies[16-18]. Omission of insulin is the most common cause of recurrent DKA and such patients (predominantly adolescents) need detailed psycho-social assessment apart from the management of the acute episode[14]. The possibility of using non-injectable "alternate systems of medicine" is a potential contribution to insulin omission in India.

Pathophysiology of DKA

Insulin deficiency coupled with glucagon excess is largely responsible for development of DKA and hyperosmolar hyperglycemic state (HHS) in patients with uncontrolled diabetes[19,20]. A decreased insulin: glucagon ratio results in reduced hepatic activity of phosphofructokinase-2 (PFK-2) and increased activity of fructose-2,6-bisphosphatase. The concentration of fructose-2,6-bisphosphate, a key activator of phosphofructokinase-1 (PFK-1, an enzyme that regulates glycolysis) is thus reduced, resulting in inhibition of