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SECOND EDITION

Clinician's Handbook of DIABETES

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Clinician's Handbook of DIABETES

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SECOND EDITION

Clinician's Handbook of DIABETES

by the PRIMER Academy of Medical Sciences

Krishna G Seshadri
Prasanna Kumar KM
GR Sridhar
Aravind Sosale

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Clinician's Handbook of Diabetes - 2nd Edition

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Preface

Case-based discussions are a unique method of understanding disease manifestations and their management. The second edition of the *Clinician's Handbook of Diabetes* is brought to you by Primer Academy of Medical Sciences (PAMS) – an academic wing of PRIMER. Encouraged by the overwhelming response to our first edition which went through two reprints, we are glad to present the second edition here. This book is targeted at family physicians, postgraduates, and clinicians who can identify similar patients in their day-to-day practice. Senior diabetologists and endocrinologists with rich experience of managing such patients have discussed the management approach based on current guidelines and their personal experiences. The authors have updated the case studies adding new dimensions to the management. New chapters include a comprehensive approach to the diabetic foot.

We would like to thank all the authors who have contributed in making this book and Macmillan Publishers for bringing out the book in a compact and concise manner.

A special thanks to Dr. Varshaa Ashish for her untiring efforts in bringing out this book in scheduled time.

The approach to any case and discussion is solely the personal view of the authors and is not the opinion of Editors or PAMS.

The Editors

About the Academy

About PRIMER Academy of Medical Sciences

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4. In collaboration with professional societies like the American Diabetes Association (ADA), the European Association for the Study of Diabetes (EASD) and other organizations that foster continuing education and research initiatives worldwide, PAMS conducts medical conferences on a large scale to provide adequate platform to medical professionals to receive latest updates in Diabetes and other allied health sciences.
5. PAMS follows the mission statement to:
    a. conduct and carry on clinical research as well as research in Basic Sciences
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Contents

CHAPTER 1

Screening and Diagnosis of Diabetes

Krishna G. Seshadri

Section 1. Who Should be Screened?

Question 1

A 40-year-old Indian male works for a multinational firm. As part of the benefit package, he is offered a screening program for diabetes. He is of otherwise good health, with no other significant medical illness. There is no family history of diabetes or coronary artery disease. He does not smoke and does not consume alcohol. He does not exercise. He is 172 cm tall and weighs 74 kg. Waist measurement is 90 cm. He requests your opinion on whether he should take the screening examination. Which one of the following statements represents the correct approach to this patient?

(a) Screening is not required as the patient is asymptomatic.

(b) Screening is not required as the patient does not have any risk factors.

(c) Screening is recommended because of the ethnicity and the presence of risk factors.

(d) Screening is required but must be done after the patient is started on lifestyle changes and an exercise regimen.

Discussion

The global rise of diabetes as a public health threat has been well documented. Two cross-sectional studies in the urban South Indian population show that the prevalence in adults over 20 years had risen 8.3% in 1989 to 11.6% in 1995.[1] The prevalence in six major cities across India in the year 2000 was estimated to be 12.1%.[2] There are three main approaches to screening. *Population-based* screening programs attempt to screen each and everyone. Targeted or selective screening is aimed at a subgroup of the population with a high risk. Opportunistic screening is done during routine visits of patients to healthcare procedures.

Screening for a disease in a population is generally done when the following criteria are met:

- The disease represents an important health problem that imposes a significant burden on the population.
- The natural history of the disease is understood.
- There is a recognizable preclinical stage during which the disease can be diagnosed.
- Treatment after early detection yields benefits superior to those obtained when the treatment is delayed.
- The benefit of screening outweighs the physical and psychological harm caused by the tests, diagnostic procedures, and treatment.
- Tests are available that can detect the preclinical stage of a disease and the tests are acceptable and reliable.
- The costs of case finding and treatment are reasonable and are balanced in relation to health expenditures as a whole. With respect to diabetes, at least six of these criteria are met in whole or in part.

Diabetes is easily diagnosed in the physician's office. Undoubtedly, it confers a high risk from premature death, microvascular and macrovascular disease. It may be undiagnosed for up to 7 years[3] and a prediabetic phase may exist for up to 12 years. In the UKPDS, 36% of patients had retinopathy at the time of diagnosis. However, the same trial noted in a different publication that both symptomatic (and therefore more likely to seek medical opinion) and asymptomatic patients have the same levels of microvascular and macrovascular disease. There are no randomized controlled trials measuring morbidity and mortality that

have conclusively demonstrated the benefit of population-wide screening for diabetes.

Various professional bodies differ in their recommendations on who needs to be screened. The American Diabetes Association recommends screening for all persons over the age of 45 or if they have risk factors. Indians are at a higher risk as an ethnic group compared to Caucasians, and diabetes occurs a decade earlier in Indians. Thus, the ICMR recommendation is to screen all Indians above 30 years of age. Other organizations, such as the United States Preventive Services Task Force (USPSTF), recommend more targeted screening. The criteria for testing in asymptomatic adults, as recommended by the ADA, are summarized in Table 1.[4] Given the high risk of the Indian community *per se* for diabetes, there should be a low threshold for screening for diabetes. Obesity confers an exponential risk for the development of diabetes. A body mass index (BMI) of 23 as the cutoff for the identification of obesity in the Indian population has been suggested.[5] The presence of a relative with diabetes confers a 40–50% lifetime risk, whereas gestational diabetes confers a 40–70% lifetime risk. Polycystic ovarian syndrome (PCOS) doubles the risk of developing diabetes.

Table 1. Tests characteristics and diagnostic values

Name of the test	Collection/method/issues	Diagnostic value
Fasting glucose	Plasma preferred. Collection should be preferably in fluoridated tubes Overnight fast required. Water may be taken ad libitum Hexokinase or glucose oxidase methods used	>125: Diabetes 100−125: Impaired fasting glucose
OGTT	Three days unrestricted diet; overnight fast 75 g of anhydrous glucose dissolved in 200–300 mL of water is given; samples drawn at 2 hours. (Intermediate values not useful.) Collection done in fluoridated tubes	>200: Diabetes 140–199: Impaired glucose tolerance
Glycosylated hemoglobin (GHb)	Random sample sufficient The labs participation in a standardization program is required Do not use in severe iron-deficiency or hemolytic anemia	>6.5: Diabetes 5.7–6.4: Increased risk for diabetes

Critique of Question 1

Correct Response: c

The person is a 40-year-old asymptomatic man. However, he is obese (by any definition) and is inactive, both of which put him at a higher risk for prediabetes and diabetes. Screening is clearly indicated in this person.

Clinical Summary for Practice

There is no clinical evidence to support universal screening for diabetes. Patients with risk factors must be screened. In these patients, triennial screening is recommended.

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Section 2. Tests for Screening and Diagnosis of Diabetes

Question 2

A 44-year-old man has a fasting plasma glucose done as part of a master health check-up offered by a national lab in his company. He is asymptomatic with no significant medical illness. Fasting plasma glucose is 145 mg/dL. Which one of the following is the most appropriate in confirming the diagnosis of diabetes in this patient?

(a) Repeat fasting plasma glucose

(b) Order a 2-hour post-load plasma glucose

(c) Order a glycosylated hemoglobin (GHb)

(d) Confirmation is not required as the plasma glucose is more than 15 mg/dL above the upper limit of normal.

Discussion

Various tests have been proposed to screen for and establish a diagnosis of diabetes. Some of these are based on scores derived from questionnaires, others look further into proteomics. At this time, however, only two sets of tests are recommended by various professional bodies – those that are based on measurement of glucose and those that are based on glycosylated HbA_{1C}.[1] The tests do not necessarily detect diabetes in the same individuals.

Fasting Plasma Glucose (FPG)

It is a simple measurement of glucose obtained after at least 8 hours (usually overnight) fasting. An FPG level of more than 126 mg/dL (repeated twice) is required to diagnose diabetes, and values between 100 and 126 mg/dL are indicative of an increased risk for diabetes (impaired fasting glucose or IFG). It is easy to perform, inexpensive, and relatively risk-free. It has better intraindividual reproducibility than 2-hour plasma glucose. Downsides include a requirement to fast and the need to process and perform test within 2 hours of collection. In addition, its sensitivity to diagnose diabetes is considerably lower when compared with the 2-hour postglucose test (2hPG). However, the FPG correlates significantly with diabetes complications, particularly retinopathy at the accepted threshold of diagnosis.

Random Plasma Glucose (RPG)

It is also referred to as casual plasma glucose and is easy to obtain in clinical practice. A value of greater than 200, when associated with polyuria, polydipsia, and unexplained weight loss, is indicative of diabetes and requires a second definitive test to confirm the diagnosis. Values between 140 and 199 mg/dL are suggestive of an increased risk for diabetes. A value of greater than 200 mg/dL is highly specific; RPG, however, is quite insensitive. At present, its use must be limited as a rapid, anytime test with high specificity in highly symptomatic patients.

Oral Glucose Tolerance Test (OGTT)

It has been the diagnostic test of choice for diabetes for 88 years. A diagnosis of diabetes is made if 2hPG value is greater than 200 and values between 140 and 199 are indicative of impaired glucose tolerance which is high risk for diabetes. The OGT identifies more individuals than FPG and correlates well with complications. It is, however, cumbersome to administer and has poor reproducibility.

Capillary Blood Glucoses (CBG)

It is useful for self-monitoring of glucose; there is, however, significant meter imprecision and substantial difference between meters to recommend it as a diagnostic or a screening tool. Any abnormality detected by CBG testing should be confirmed with laboratory testing.

Glycosylated Hemoglobin

It is derived from the nonenzymatic addition of glucose to valine and lysine residues on the α- and β-chains of the hemoglobin molecule. HbA_{1C} is a specific GHb that results from the attachment of glucose to the N-terminal valine of the hemoglobin β-chain. The concentration of HbA_{1C} depends on both the concentration of glucose in the blood and the lifespan of the erythrocyte. Because erythrocytes are in the circulation for approximately 4 months, HbA_{1C} represents the integrated glucose concentration over the preceding 2−3 months.[2] It has been widely used as a test for assessing the efficacy of therapy as well as a prognosticator for over 2 decades. In 2010, the American Diabetes Association recommended the use of HbA_{1C} as a screening and diagnostic test.[3] A value of greater than 6.5 is considered diagnostic of diabetes. Values between 5.7 and 6.4 are considered to represent a category of patients at an increased risk for diabetes. Although A_{1C} is the strongest

prognosticator for the complications of diabetes, its utility as a diagnostic tool is under some challenge. Importantly, there is significant variance in methodology and standardization of the test. Several conditions affect the test including iron-deficiency anemia, hemolysis, and uncontrolled hypothyroidism. One-third fewer patients are diagnosed with diabetes with the accepted threshold of 6.5 when compared with a fasting glucose of 126 or above. However, it is expected that the greater practicality of the test will actually increase the number of patients diagnosed.

The capillary blood A_{1C} test which is now available, and also called point-of-care (POC) A_{1C} testing, has utility in monitoring glycemic control. It has not, however, been studied adequately as a screening or diagnostic tool.

What Test should be Used?

Before choosing a test, it is important to consider the characteristics of the test, the availability of the test, and its standardization in the lab and its ease and acceptability of use in your practice. Glucose-based tests are cheaper but require restrictions of food and timing. HbA_{1C} does not have these restrictions but is limited by the need for standardization, and cannot be used in certain conditions. HbA_{1C} is highly reproducible whereas 2hPG is the least reproducible.

Irrespective of the test used, it must be repeated to confirm the presence of diabetes. When two different tests are available as is often the case, the one with the higher value must be repeated, for example, the patient has come to your office with an HbA_{1C} of 6. 3 and an FPG of 135, the FPG must be repeated. Discordant values are most often found in patients with borderline numbers and clinical follow up for 8−12 weeks with repeat testing is sufficient.

Critique of Question 2

Correct Response: a

Unless the diagnosis is clear or the patient is symptomatic, confirmation of the diagnosis by repeat testing is recommended. For the purpose of diagnosis alone, repeating the same test is sufficient (option “a”). Other tests including HbA_{1C} may be required as part of the initial evaluation but are not essential to establish the diagnosis. When more than one test is available, repeating the test with the higher value is recommended.

Clinical Summary for Practice

Fasting plasma glucose, glucose estimation 2 hours after a glucose load, or GHb are all acceptable tests for the diagnosis of diabetes. The choice of the test depends on the patient's convenience and the ability of the local laboratory to perform the test accurately. A single value must not be considered diagnostic; the test must be repeated. An FPG greater than 126 or a postglucose value of 200 or an HbA_{1C} of greater than 6.5 is considered diagnostic of diabetes.

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Practice Box

1. Who should be screened for diabetes?
   (a) Age over 30 years
   (b) BMI > 23
   (c) Family history of diabetes
   (d) Previous GDM
   (e) Polycystic ovarian syndrome
2. What tests should be done?
   (a) Fasting plasma glucose
   (b) 2-hour PG after an oral load of 75 g
   (c) HbA_{1C} (sensitivity is lower in the Indian population when ADA cut-offs are used)

   Two values are required for confirmation
3. What are the diagnostic cut-offs?
   (a) Diabetes: FPG > 126 or 2-hour PG > 200 or HbA_{1C} >6.5
   (b) Increased risk for diabetes: HbA_{1C} 5.7–6.4, FPG >100 (impaired fasting glucose) 2-hour PG > 140 (impaired glucose tolerance)

CHAPTER 2

Prevention of Diabetes Mellitus

GR Sridhar

Section 1. How can Diabetes Mellitus be Prevented?

Question 1

A 36-year-old man visits his physician and enquires whether diabetes can be prevented; he is concerned because of his gradually increasing weight, approaching the age of 40, on the background of both his parents having diabetes mellitus. The subject is 176 cm tall and weighed 82 kg. He smokes and has lunch at the office canteen 4 days a week. Since he has to work at the computer nearly a third of a day, he has no physical activity at work nor does he have the time and until now inclination for recreational activity. His fasting plasma glucose measured 118 mg/dL and 2-hour postprandial 162 mg/dL. HbA_{1C} was 6.3%. Which one of the following could be most effective in halting the progression to diabetes in this patient?

(a) Lifestyle changes only
(b) Lifestyle changes and metformin
(c) Lifestyle changes and pioglitazone
(d) Lifestyle changes and glimepiride
(e) Lifestyle changes and basal insulin

Discussion

Diabetes mellitus is common, increasing, and debilitating. However it has a long preclinical phase which can be identified; methods, which can be widely applied without incurring a lot of money, are available. It is said that we are ineffective in preventing diabetes, not because we do not have evidence but because we do not know how to put the evidence to practice.[1]

Risk factors that can be changed are known – overweight, obesity, sedentary life habits, hypertension, low high-density lipoprotein (HDL-C) cholesterol, elevated triglycerides (insulin resistance), smoking, and dietary indiscretion.[2]

Lifestyle Interventions

Intuitively, economically, morally, and socially, prevention is considered better than treatment or cure. Diabetes is particularly suited for preventive efforts; it is of gradual onset starting perhaps in utero and progressing as age advances. Evidence that lifestyle changes prevent or postpone type 2 diabetes were obtained by studying individuals with the highest risk of developing diabetes viz., those with impaired glucose tolerance (IGT), which is one stage before type 2 diabetes. Lifestyle changes aimed to achieve and maintain normal body weight by diet and exercise. Dietary regulation included reduction in fat intake, increased vegetable consumption; physical exercise was 30−40 minutes of moderate activity on most if not all days of the week.[2]

Both the initial observational studies (Malmo Study in Sweden and Da Qing Study) and the subsequent randomized control trials support that lifestyle changes can postpone or prevent the onset of diabetes. The Finnish Diabetes Prevention Study involved 522 obese or overweight subjects who were followed up for 3.2 years and showed that at 2-year follow up, the incidence of type 2 diabetes was decreased by half in those who were individually counseled to maintain normal body weight, reduce fat intake, and increase physical activity. The addition of moderate leisure time physical activity (LTPA) compounded the benefits seen and was proportional to the strenuousness of the activity.

The Diabetes Prevention Program is the largest randomized controlled prevention trial (RCT) with more than 3000 US American adults enrolled. In this study, lifestyle intervention and metformin were both effective in preventing type 2 diabetes mellitus; lifestyle was better in older adults. The lifestyle intervention group also had lower mortality. The Indian Diabetes Prevention Program also showed similar results: lifestyle modification and metformin both and together reduced the incidence of

Table 1. Effectiveness of lifestyle interventions in type 2 diabetes

Study	Risk reduction (%)	Follow-up risk reduction (%)
Da Qing Study, China	31–46	43
Diabetes Prevention Study, Finland	58	43
Diabetes Prevention Program, USA	58*	34
Indian Diabetes Prevention Program	28.5†	–

*39% in the metformin group; †26.4% in the metformin group.

diabetes (risk reduction was 28.5% with lifestyle, 26.4% with metformin, and 26.4% with the use of both; Table 1).[3]

A promising finding from these trials is that lifestyle interventions lasting for a limited time period seem to have a long-lasting carryover effect on type 2 diabetes incidence. In the Diabetes Prevention Study for instance, after a median of 7 years total follow up, a marked reduction in the cumulative incidence of type 2 diabetes was sustained. The relative risk reduction during the total follow up was 43%.

Drug Therapy

Although lifestyle interventions resulting in weight loss was shown to be the most effective, in real life, not all individuals can adhere to the advice and achieve weight loss. Are there options for this large group of people? Drugs? Results from DPP suggested that drugs may be considered as add-on or a secondary intervention to follow in conjunction with lifestyle intervention.[2] Metformin, used in the Diabetes Prevention Program (DPP; 850 mg twice a day), was most effective in more obese participants (baseline BMI >35 kg/m^2), who experienced a 53% reduction in diabetes incidence, and in those younger than 45 years of age, who saw a 44% reduction. It was of little benefit in older individuals; 60–85 years of age at baseline. The effectiveness of metformin was attributed in part to weight loss, which averaged 1.7 kg and accounted for 64% of its beneficial effect. Contraindications to metformin and GI side effects limit its use; it is less effective in those with low BMI. Acarbose, used in the STOP-NIDDM Trial, reduced the conversion of IGT to diabetes and also appeared to lower the risk of future coronary events, although they were few in absolute numbers. It is associated with GI side effects. Troglitazone, the first glitazone (TRIPOD Study) and rosiglitazone (DREAM Study) were shown to effectively prevent the progression to diabetes mellitus, but both drugs have been taken off the market.

Translating Evidence into Practice

How can the results of these trials be put into practice? The first step in diabetes prevention is identifying patients who are at the highest risk. This group includes individuals of any age who are overweight and obese (BMI > 25 kg/m^2) with at least one risk factor (such as high-risk ethnic group, first-degree relative with diabetes, personal history of gestational diabetes, or sedentary lifestyle). In such individuals, setting and achieving modest real-world goals is the key. In the Finnish study, none of the patients with IGT who reached four of the following five predefined lifestyle targets developed diabetes:

- Weight loss >5%
- Intake of fat <30% of energy
- Saturated fats <10% energy
- Decreased dietary fat ≤15 g/1000 kcal
- Increased physical activity to 4 hours/week.[4]

These are fairly modest goals that can be achieved. To practice such a lifestyle is feasible for the long term.[5] Lifestyle intervention in these clinical trials had strong focus on increased physical activity (2.5–4 hours/week) and dietary modification (increased whole grains, fiber, vegetables, and fruit; reduced total and saturated fat, sugar, and refined grains). The interventions used behavior modification techniques, such as motivational interviewing, self-monitoring, and individualized short- and long-term goals. It must be pointed out that although most of these studies did focus on weight loss, benefit was seen even if weight loss was not achieved. It has been estimated that when 6.4 persons undergo lifestyle modifications one new case of diabetes is prevented [(number needed to treat (NNT) = 6.4 over 4–6 years follow up)]. This is remarkable when compared with the effectiveness of other interventions in medicine. It is also important to address multiple risk factors as a combination of risk factors may compound the risk for diabetes.

For patients who are unable to achieve these lifestyle goals or those who progress despite exercising and losing weight, metformin has proven to be effective, especially in younger obese patients. However, none of these medications have as robust evidence in diabetes prevention as lifestyle intervention strategies have. In addition, withdrawal of medications partially restores the risk of progression to diabetes.[6]

Implementation

Diabetes cannot be prevented in the consulting room alone. A coordinated effort is needed involving the individual, the family, as well as the society. National prevention programs are imperative. The Finnish National Diabetes Prevention Program took

up the FIN-D2D in a population-based high-risk and early treatment strategies. The European Union developed a DE-PLAN initiative to develop evidence for diabetes prevention practice in 17 European countries. The IMAGE Project developed a "toolkit" for the prevention of type 2 diabetes mellitus. The kit provides information and guidance on management, financial, intervention, quality assurance based on the latest scientific evidence. A web-based organization is available called "Who is active in diabetes prevention" (www.activeindiabetesprevention.com) where there is an exchange in experience in preventing type 2 diabetes mellitus. Prevention of diabetes is our most powerful intervention, and successful implementation of these proven strategies should be the focus of our effort.

Critique of Question 1

Correct Response: b

Lifestyle modifications must be offered to all persons enrolled in a prevention program. In patients, such as the one presented here, who are at the highest risk for type 2 diabetes including impaired fasting glucose (IFG), IGT, and an HbA_{1C} of more than 6, pharmacotherapy may be added either simultaneously or if lifestyle fail to achieve goals. Although the glitazones, especially troglitazone and rosiglitazone, have demonstrated efficacy in preventing diabetes in clinical trials, safety concerns have prompted their withdrawal from the market and hence, at this time, glitazones are not recommended. Sulfonylureas, in general, have not demonstrated efficacy in prevention of diabetes. The concept of β-cell rest by administering insulin to prevent diabetes is attractive, and the ORIGIN Study has shown that use of basal insulin to individuals at high risk of developing cardiovascular disease was effective in preventing significant rise of HbA_{1C} and progression to diabetes mellitus.[7] A discussion about the option, efficacy, and convenience of insulin compared with lifestyle and metformin is in order. Acarbose is an alternative, but has less robust data.

Clinical Summary for Practice

Diabetes is preventable. The key issue seems to be a comprehensive approach to correct several risk factors simultaneously. Lifestyle modifications provide the greatest reduction in progression to diabetes. All high-risk individuals must be encouraged to modify their lifestyle to achieve modest weight reduction, limit calories and fat, and include up to 4 hours of exercise every week. Selected patients with both impaired fasting glucose and IGT may be considered for addition of metformin.

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Practice Box

1. Identify patients at high risk for diabetes for prevention strategies. These include:
   (a) patients with IFG or IGT
   (b) strong family history of diabetes
   (c) BMI > 23 or waist > 88 in men or 80 in women
   (d) previous history of gestational diabetes or PCOS
   (e) age > 40 years
2. The objective of preventive strategies to prevent or delay progression to diabetes.
3. Lifestyle is the key. The objective of lifestyle changes should be:
   (a) weight loss >5%
   (b) intake of fat <30% of energy
   (c) saturated fats <10% energy
   (d) decreased dietary fat ≤15 g/1000 kcal
   (e) increased physical activity to 4 hours/week
4. Medications have an adjunct role. Metformin is widely used. At this time, it is recommended for patients who have both a fasting glucose > 100 and a post-glucose value of > 140.
5. A GAME PLAN education program based on the resources used in the Diabetes Prevention Program is available for use freely at the following website: http://www.ndep.nih.gov/publications/PublicationDetail.aspx?PubId=118

CHAPTER 3

Initial Approach to a Patient with Diabetes

Subhankar Chowdhury

Section 1.

Question 1

A 25-year-old software engineer has come to you with incidentally detected hyperglycemia during a routine medical evaluation prior to job placement. He is otherwise asymptomatic. Both of his parents were diagnosed with diabetes 3 years back and both of them are overweight. He is very much worried about his diabetes and thinks that he may require insulin, which is going to interfere with his quality of life. His physical examination is unremarkable except for a body mass index of 31 kg/m^2 and presence of acanthosis over the nape of neck. His fasting and 2-hour postprandial (PP) glucose values are 164 and 269 mg/dL, respectively; HbA_{1C} is 7.8%. Which one of the following choices is correct regarding his initial management?

(a) This patient needs to be started on multiple oral drugs for diabetes control.

(b) The patient is unlikely to have complications of diabetes as he is asymptomatic.

(c) Diabetes self-management education (DSME) with/without metformin may improve his quality of life and help reach target HbA_{1C}.

(d) Type 1 diabetes is a reasonable probability in this young patient.

(e) Bariatric surgery is another option in this patient as it may cure his diabetes.

Discussion

The current evidences show that early and intensive glycemic control prevents or delays the long-term micro- and macrovascular complications of diabetes. Early achievement of euglycemia may also delay the progressive β-cell failure in type 2 diabetes. In the DCCT/EDIC study (involving type 1 diabetes),[1] initial improvements in glycemic control led to microvascular benefits and both micro- and macrovascular risk reduction in the long run. In the UKPDS 10-year follow up (involving type 2 diabetes)[2], continued reduction in microvascular complications as well as reductions in the risk of myocardial infarction (MI) and diabetes-related death was observed in the formerly intensively treated group, possibly due to the so-called "metabolic memory" effect. The ACCORD[3] and ADVANCE[4] studies also indirectly recommend early control of diabetes as we may not have an opportunity once cardiovascular (CV) disease sets in. The initial presentation is also a good opportunity to assess the patient's CV risk factors and presence of complications. It is important to appreciate that patients of diabetes, especially type 2, may have a long asymptomatic phase before the diagnosis; this means that onset may have preceded diagnosis by even several years, thus making it possible for complications to be present even at diagnosis. In fact about 25–40% patients of newly diagnosed type 2 diabetes may have one or more microvascular complications. The physician should concentrate on diabetes education, achieving early and good glycemic control, delaying the progression of diabetes and existing complications and also preventing the appearance of serious complications in the course of the disease. Establishing a good rapport with the patient and his/her family ensure better long-term compliance in a chronic disease like diabetes.

Listen to Your Patient

1. Onset of diabetes – age of the patient at diagnosis
2. Asymptomatic or presence of symptoms (osmotic symptoms/complications of diabetes)
3. History of hyperglycemic emergencies (diabetic ketoacidosis, hyperosmolar coma)
4. Etiological suggestions like pain abdomen, steatorrhea
5. Precipitating events like steroid use, infection, psychological stress
6. Physical activity level (sedentary, moderate, high)
7. Diet history – binge eating habits, intake of calorie-dense fast food, average daily calorie intake

8. Addictions – smoking including tobacco chewing and alcohol consumption
9. Periods of weight gain and unintentional weight loss
10. Any recent use of antidiabetic medication and glycemic response to those medications, use of other drugs known to interfere with glucose metabolism
11. History related to complications:
    - Microvascular – blurring of vision (retinopathy), periorbital or pedal edema (nephropathy), symptoms suggestive of neuropathy (motor, sensory, autonomic including sexual dysfunction, urinary symptoms and gastroparesis)
    - Macrovascular – effort/rest angina or exertional dyspnea (coronary heart disease), hemiparesis/hemiplegia (cerebrovascular disease), claudication/rest pain (peripheral arterial disease) (PAD)
    - Others – psychosocial problems, dental and periodontal disease, bone and soft tissue rheumatism
    - Foot – history of ulcer, amputation, barefoot walking, footwear, etc.
12. Family history of diabetes in first or second degree relatives and age of onset of diabetes in them, socioeconomic status, and attitude of family members to diabetes
13. Awareness level regarding symptoms and management of hypoglycemia and diabetic complications

Look and feel

1. Height, weight, and BMI; waist circumference
2. Palpate all peripheral pulses; carotid or renal bruit; resting HR with postural changes
3. Blood pressure recording (both arms) on two separate occasions with postural change
4. Any evidence of heart failure: look for engorged neck veins, left ventricular S_3 and bi-basal lung crepitations
5. Features of insulin resistance – Acanthosis nigricans (neck and axilla) hyperandrogenism in females
6. Evidence of dyslipidemia – xanthoma
7. Hepatomegaly (may be due to nonalcoholic fatty liver disease [NAFLD]); splenomegaly
8. Skin infections, soft tissue rheumatism (“prayer hand” sign and others)

9. Cataract and diabetic retinopathy (fundus examination)
10. Associated illness (thyroid examination, anemia, edema, etc.)
11. Comprehensive foot examination – remove footwear and socks; *inspect footwear also*
    - Inspection of skin, hair, and nails for features of neurovascular insufficiency (dry skin, shiny skin, loss of hair, brittle nails, dilated veins, ulcer, gangrene)
    - Palpation of dorsalis pedis and posterior tibial pulses, ankle brachial pressure index (ABI)
    - Difference in temperature in between two feet
    - Mobility and deformity of great toe, deformities of other toes, look in between toes for intertrigo
    - Document small muscle atrophy, calluses, and foot deformities
    - Presence/absence of patellar and Achilles reflexes
    - Assessment of loss of protective sensations (LOPS) (use 10 g monofilament and sharp pin or 128 Hz tuning fork or biosthesiometer or ankle reflex)
    - Probe to bone test in presence of ulcer
    - Ideally all patients should be evaluated for toe pressure in addition to ABI. $TcPO_2$ is another important parameter, which predicts ulcer healing in diabetics
12. Always look at patient's previous reports as they may contain missed clues

Assess, ask, and confirm

1. HbA_{1C} (By a NGSP certified assay), if results are not available within past 2–3 months
2. Urine routine examination (especially for proteins, ketones, and for evidence of infection)
3. Spot urine albumin/creatinine ratio (ACR) (preferably in absence of uncontrolled hyperglycemia and uncontrolled hypertension)
4. Serum creatinine and calculated GFR/creatinine clearance (by four variable MDRD equation)
5. Fasting lipid profile, including total, LDL-C and HDL-C, and triglycerides (preferably after reasonable glycemic control); calculate CV risk by UKPDS risk engine or ACC/AHA pooled cohort risk equation

6. Liver function tests
7. Ultrasound abdomen (pancreas, liver, kidneys, post void residue)
8. TSH, anti-TPO, anti-thyroglobulin and anti-tissue transglutaminase (IgA) antibodies in type 1 diabetes patients
9. Electrocardiogram; echocardiography if ECG is abnormal or patient is symptomatic
10. C-peptide (preferably post-meal), anti-GAD65, anti-IA2 antibody and anti-insulin antibody (in insulin naïve patients) where etiology/type of diabetes is uncertain
11. Other investigations as per situation

Don't feel shy to ask for help

1. Nutritionist's advice for medical nutrition therapy (MNT)
2. DSME with diabetic educators
3. Podiatrist's help for proper foot care and rehabilitation
4. Ophthalmologist's expertise if patient has visual deterioration, severe nonproliferative retinopathy, proliferative retinopathy, clinically significant macular edema; or, more often, as a routine initial evaluation
5. Nephrology consultation in chronic kidney disease (CKD) stage 4 and 5 (creatinine clearance less than 30 mL/min/1.73m^2)
6. Specialized CV assessment and interventions for coronary artery disease (CAD) and PAD if needed
7. Dental opinion for dental caries and periodontitis
8. Psychiatrist's help for depression and adjustment disorder
9. Group therapy
10. Family planning for women of reproductive age

Special situations[5]

1. Children and adolescents may have psychological issues, which need to be addressed and risk factors for recurrent episodes of ketoacidosis and hypoglycemia should be sought and appropriate measures should be taken to correct the same.
2. Target glycemic goals should be individualized, particularly for children and older adults with advanced complications of diabetes and limited life expectancy.

3. Diabetes may be detected during pregnancy and will require more stringent glycemic control of as per recommended guidelines. In women of child-bearing potential adequate glycemic control, evaluation for micro- and macroangiopathy, and proper preconceptional care is a must.
4. Look for secondary causes of diabetes including acromegaly, Cushing's syndrome, use of diabetogenic drugs, fibrocalculous pancreatopathy with diabetes and address the cause, wherever possible.
5. In children and adolescents examination for presence of optic atrophy, diabetes insipidus, deafness, mitochondrial myopathies, somatic features of chromosomal disorders, and polycystic ovarian syndrome (PCOS) should be undertaken.

Management[5]

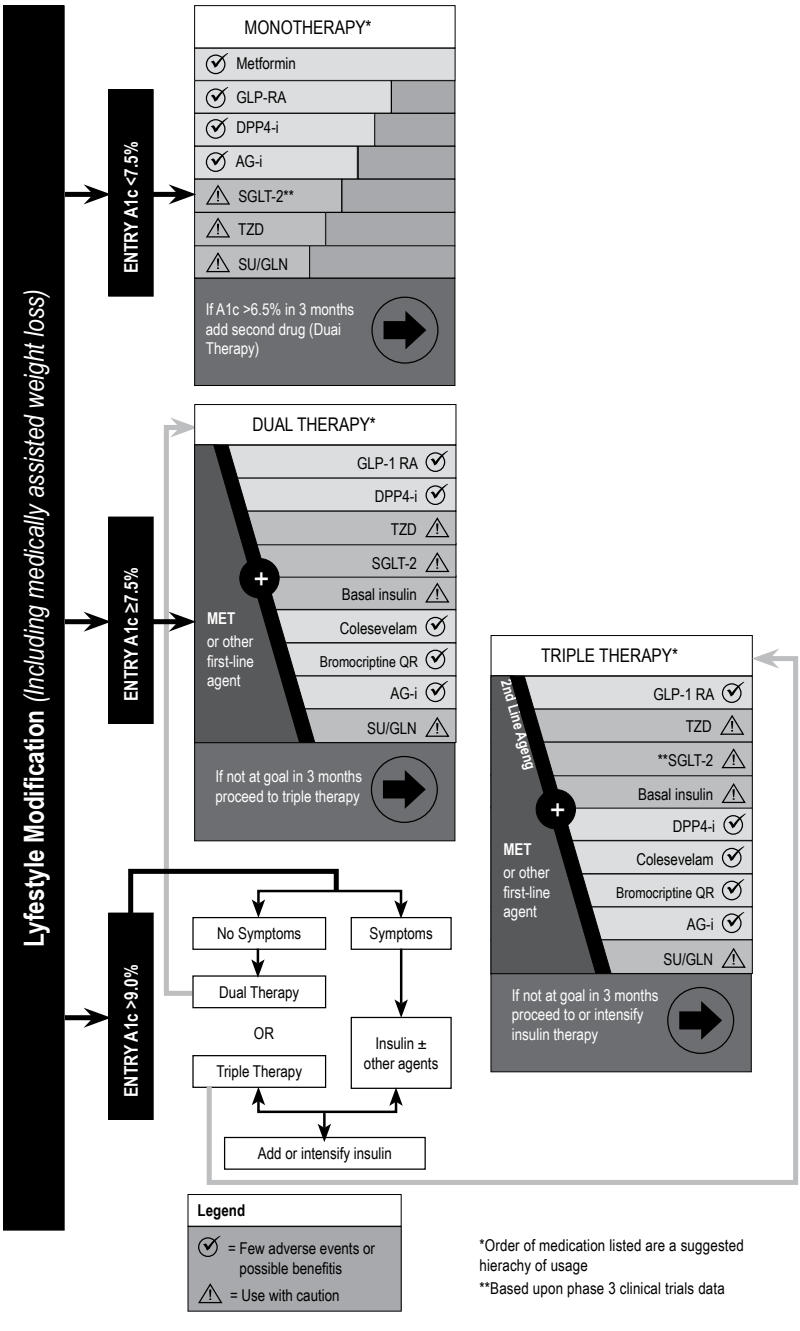
1. *Education* of patient and family is possibly the most neglected, but the most important part of management.
2. *Physical activity.* Patients should try to achieve at least 150 min/week of moderate-intensity aerobic physical activity (50–70% of maximum heart rate or brisk walking for 30 min for at least 5 days a week) and should be encouraged to perform resistance training three times per week.
3. *Nutrition.* Patients should try to adhere to MNT as advised by nutritionist.
4. *Hypertension.* A blood pressure more than or equal to 140/90 mmHg on two separate occasions confirms the diagnosis of hypertension. In addition to lifestyle management (5–10% weight loss with diet and exercise if overweight), decreasing sodium intake and increasing potassium intake, angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), and calcium channel blockers (CCB) can be used. Target BP in all patients should be less than 140/80 mmHg. However, in young individuals with long life expectancy a lower target of less than 130/80 is suggested for better renoprotection.
5. *Dyslipidemia.* Physical activity and nutrition therapy should be instituted to reduce the lipid levels. Statin therapy should be added to lifestyle therapy, regardless of baseline lipid levels for diabetic patients with overt cardiovascular disease (CVD) and for those without CVD if above the age of 40 years and have one or more other CVD risk factors. In patients less than 40 years of age having multiple risk factors or LDL-C higher than 100 mg/dL despite lifestyle modification, statin may be considered. In majority of patients

a target LDL-C less than 100 mg/dL is advised. In patients with overt CAD the target should be less than 70 mg/dL. According to the recent ACC/AHA guidelines all diabetic patients aged 40–75 years with LDL-C above 70 mg/dL should be put on statin and the target should be 30–50% reduction of LDL-C from the baseline.

6. *Antiplatelet agents*. Consider aspirin therapy (75–150 mg/day) as a primary prevention strategy in those with type 1 or type 2 diabetes at increased CV risk (10-year risk >10%). This includes most men >50 years of age or women >60 years of age who have at least one additional major risk factor (family history of premature CVD, hypertension, smoking, dyslipidemia, or albuminuria). Aspirin therapy (75–150 mg/day) is used as a secondary prevention strategy in those with diabetes with a history of CVD. Clopidogrel can be offered if there is aspirin-allergy or, active peptic ulcer disease. Clopidogrel may be preferable to aspirin in presence of PAD.
7. *Addictions.* Patients should be encouraged to stop smoking (in fact quit tobacco in any form); appropriate counseling and medical support may be given. Alcohol should be avoided and if that is not possible, daily intake should be reduced to maximum two units for males and one unit for females.
8. *Nephropathy.* Reduction of protein intake to 1.0 g/kg body wt/day in individuals with diabetes and the earlier stages of CKD and to 0.8 g/kg body wt/day in the later stages of CKD may improve measures of renal function (urine albumin excretion rate and GFR), particularly if there is inadequate response to ACEI/ARB. In the treatment of the nonpregnant patient with micro- or macroalbuminuria, either ACE inhibitors or ARBs should be used.
9. *Retinopathy.* Promptly refer patients with any level of macular edema, severe nonproliferative diabetic retinopathy or proliferative diabetic retinopathy to an ophthalmologist for laser photocoagulation and other appropriate treatment.
10. *Neuropathy.* Medications for the relief of symptoms related to distal polyneuropathy (amitryptiline, duloxetine, pregabalin) and autonomic neuropathy are recommended, as they improve the quality of life of the patient.
11. *Foot care.* Patients with loss of protective sensation (LOPS) should receive general foot care education. They should be prescribed preventive and therapeutic footwear. Those with ABI <0.4 or any ABI with toe pressure <40 mmHg or $TcPO_2$<45 should be referred to specialists vascular surgeons for management.

Initial management of hyperglycaemia[5,6]

1. Individualization of glycemic targets and goals is very important.
2. Young newly diagnosed type 2 diabetes patients with no evidence of advanced complications should aim for the HbA_{1C} target of less than 6.5%, that is, HbA_{1C} as close to normal as can safely be achieved without causing hypoglycemia or marked weight gain. HbA_{1C} should be monitored every 3–4 months. However, after stabilization and if there is no change in medications, HbA_{1C} may be done twice a year.
3. Most of the current guidelines recommend metformin therapy along with lifestyle modification from the outset. However, we believe a trial of lifestyle modification is preferable, particularly if the patient is asymptomatic and HbA_{1C} is between 7% and 8.5%; drug treatment should be added if glycemic goals are not achieved within 3 months.
3. Metformin is generally the initial and also the cornerstone of drug therapy if there is no contraindication to its use. Among all the oral medications, metformin is the only drug which is known to reduce CV mortality.
4. If targets are not met within 3 months, therapy may be intensified by adding new drugs to the regimen as per guidelines; these may include sulphonylureas/glinides, glitazones, DPP-4 inhibitors, α-glucosidase inhibitors, GLP-1 analogues, and eventually insulin. However, if the presenting blood glucose is high, patients may be put on combination therapy from the very beginning.
5. If patient is grossly symptomatic with significant weight loss and weakness, fasting glucose levels above 300 mg/dL or HbA_{1C} above 9–10% or, there is significant systemic infection like pulmonary tuberculosis or, significant hepatic, renal or, cardiac failure or, in a young lady contemplating pregnancy, insulin should generally be a part of initial therapy along with lifestyle modification.
6. Self-monitoring of blood glucose (SMBG) should be carried out three or more times daily by patients using multiple insulin injections or insulin pump therapy. For patients using less frequent insulin injections, noninsulin therapies, or medical nutrition therapy alone, SMBG may still be useful as an important educational tool and also as a guide to the success of therapy. Patient should be taught not only the technique, but also how to adjust therapy on the basis of SMBG. SMBG before exercise, high-risk sports, or driving provides additional confidence.


Lyfestyle Modification (Including medically assisted weight loss)
ENTRY A1c <7.5%
MONOTHERAPY*
Metformin
GLP-RA
DPP4-i
AG-i
SGLT-2**
TZD
SU/GLN
If A1c >6.5% in 3 months add second drug (Duai Therapy)
ENTRY A1c ≥7.5%
DUAL THERAPY*
MET or other first-line agent
GLP-1 RA
DPP4-i
TZD
SGLT-2
Basal insulin
Colesevelam
Bromocriptine QR
AG-i
SU/GLN
If not at goal in 3 months proceed to triple therapy
ENTRY A1c >9.0%
No Symptoms
Symptoms
Dual Therapy
OR
Triple Therapy
Insulin ± other agents
Add or intensify insulin
TRIPLE THERAPY*
2nd Line Agent
MET or other first-line agent
GLP-1 RA
TZD
**SGLT-2
Basal insulin
DPP4-i
Colesevelam
Bromocriptine QR
AG-i
SU/GLN
If not at goal in 3 months proceed to or intensify insulin therapy
Legend
= Few adverse events or possible benefitis
= Use with caution
*Order of medication listed are a suggested hierachy of usage
**Based upon phase 3 clinical trials data

Critique of Question 1

Correct Response: c

Studies have shown that DSME is associated with improved knowledge of diabetes and its complications, proper self-care behavior, better clinical outcomes such as lower HbA_{1C}, lower self-reported weight, and improved quality of life.[5] Patients with minimal hyperglycemia without overt symptoms or complications should be put on lifestyle modification. Available guidelines also recommend metformin therapy in addition to lifestyle modification from the very beginning. Many patients with type 2 diabetes have evidences of complications at the time of diagnosis and a thorough search should be made for complications.

In view of his obesity, presence of acanthosis, and family history he is most likely to have type 2 diabetes. Type 1 diabetes is unlikely as patient is asymptomatic, obese, has biparental diabetes, and only moderately hyperglycemic.

Bariatric surgery should be considered for adults with BMI >35 kg/m^2 and type 2 diabetes, especially if the diabetes or associated comorbidities are difficult to control with lifestyle and pharmacologic therapy. There is currently insufficient evidence to generally recommend bariatric surgery in patients with BMI<35 kg/m^2.

Clinical Summary for Practice

All patients with diabetes at presentation should be evaluated with detailed history and thorough examination with particular emphasis on the risk factors for diabetes and complications of diabetes. Having done that, an appropriate lifestyle plan should be drawn for them, which consists of healthy eating and appropriate physical activity; avoidance of tobacco and moderation (if at all) of alcohol intake should also be implemented. An appropriate HbA_{1C} target should be set and antihyperglycemic agents should be used to achieve that target without producing significant hypoglycemia. Care should be taken to provide appropriate therapy for hypertension, dyslipidemia, and other CVD risk. If complications of diabetes are present, treatment should be initiated and measures should be taken to prevent further progression of existing or development of new complications. However the cornerstone of therapy is DSME supplemented by regular monitoring of glycemic parameters and nonglycemic risk factors and, above all, compliance to therapy.

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CHAPTER 4

Diabetes and Lifestyle Modification

TA Vidya

Section 1.

Question 1

A 32-year-old woman has been newly diagnosed with diabetes. She weighs 69 kg and has a BMI of 27 kg/m². Her HbA_{1C} is 8.1% and BP is 120/80 mmHg. She is well educated, but from a highly conservative family. She has looked up some medical websites and argues that her BMI is not in the obese range according to them, so can she do yoga at home instead of walking for exercise. Which of the following is appropriate for this patient?

(a) Nutrition therapy is adequate for her BMI.
(b) Aim for ideal body weight as patient is young.
(c) Weight loss of 3–5 kg.
(d) Yoga at home daily as sole exercise therapy as per her wish.
(e) Bariatric surgery.

Discussion

There is an increased association of obesity, especially central obesity with type 2 diabetes mellitus (T2DM). Central obesity is linked to increased insulin resistance and the metabolic syndrome and its attendant risk for cardiovascular disease. It is recognized that in South Asians, risk of diabetes and its complications is found at

a lower BMI level than the original ones set for predominantly western/Caucasian populations.[1]

Management of obesity is therefore an important aspect of T2DM. Adequate motivation and guidance should be given to every patient with the aim of achieving an acceptable body weight, and eventually physical fitness.

In overweight and obese people, weight loss improves glycemic control. Moderate weight loss can improve insulin action and decrease fasting blood glucose concentrations. Weight loss of up to 5–10% of the baseline weight results in improvement of metabolic parameters like glucose levels, lipid levels and BP, and reduction in inflammatory markers.

When a weight loss regimen is initiated, the initial weight loss results from reduction in caloric intake. An energy deficit of 500–1000 kcal/day leads to a weight loss of up to 1 kg/wk and an average weight loss of 8% after 6 months. This amount of weight loss is sufficient to reduce glucose levels, blood pressure, and improve hyperlipidemia.[2]

Most people who lose weight eventually regain a proportion or all of the lost weight. Therefore, caloric restriction should be accompanied by a structured regimen of adequate physical activity.

Physical activity of 150 minutes per week is recommended for all adults. Exercise has benefits beyond lowering blood glucose like reducing depression, increasing fitness levels, etc. For adults who need to lose weight, 60–75 minutes of moderate-intensity activity (moderately quick walking) or 35 minutes of vigorous activity (e.g., jogging) daily is needed to maintain long-term weight loss.[3]

The level at which the patient starts exercise is determined by the current fitness levels. In appropriate patients, assessment of cardiac capacity and autonomic neuropathy should be done and exercise regimen should be initiated accordingly. It is also recommended that a modest level of anaerobic exercise be added to the regimen in T2DM. This helps in maintaining muscle mass which in turn maintains insulin sensitivity.[3] Yoga and other alternative exercise regimens like tai chi are milder forms of exercise. At present, they are not recommended as sole exercise prescription in T2DM.[1]

Since the exercise has to be sustained over a long period (essentially lifelong), it is better to choose those which are accessible, appropriate, and acceptable to the patient.

Surgery to promote weight loss, such as gastric bypass surgery or bariatric surgery, is recommended only when BMI ≥ 40 or BMI ≥ 35 and other major comorbidities

are present. In the Indian context, bariatric surgery is recommended for patients with BMI ≥ 37.5 or for patients with BMI ≥ 32.5 with other comorbidities.[4]

Critique of Question 1

Correct Response: c

Most adults will find it difficult to attain ideal body weight. Patients on sulfonylureas or insulin may actually gain weight. Also overweight adults who have lost weight before detection of hyperglycemia may gain weight once glycemic control is achieved. Therefore it is better not to target ideal body weight; 5–10% loss of current body weight leads to improvement in various metabolic parameters. It is an achievable target for many patients and also one that can be sustained reasonably in the long run. So this is the target for weight loss in most diabetic patients.

Clinical Summary for Practice

In patients with T2DM who are overweight or obese, lifestyle modifications are recommended with a view to reducing weight and improving metabolic parameters. A modest weight loss of 5–10% of the baseline weight is the aim. This is best achieved through a combination of reduction in daily caloric intake and a structured exercise program. Sustained weight loss and improvement in physical fitness are long-term goals. The caloric reduction is achieved through reduction of calorie-dense foods such as fats and increase in consumption of complex carbohydrates and fiber-rich food in the form of fruits and vegetables. A combination of aerobic and anaerobic exercises is tailor-made for the patient after making sure that patient is physically fit for the regimen. Patient should be periodically monitored for compliance and motivated to continue in his efforts.

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Section 2.

Question 2

A 35-year-old homemaker, BMI 28.1% and weight 62 kg, has been diagnosed with T2DM. Which of the following is the most appropriate advice you can give her?

(a) To forgo 1 meal/day so that she can lose weight quickly.

(b) Limit portion sizes of cereals and meat, stop snacking on junk foods.

(c) Cook a separate diabetic diet meal for herself to ensure compliance.

(d) She should stick to a diabetic diet, but need not deprive herself as she can eat "diabetic snacks/fat-free foods"

(e) To adopt a high protein, low carbohydrate diet

Discussion

In diabetes, the ability of the body to metabolize the different groups of foodstuffs and efficiently dispose of the glucose load is impaired. The excess glucose accumulates in the blood and is excreted in urine. If this is high enough, uncontrolled hyperglycemia occurs, patient may lose weight, and ketogenesis may occur.

The principle of diet therapy in diabetes is to provide only as much calories daily as are needed to maintain metabolism. This is calculated for each person based on the patient's present body weight, ideal body weight, and the amount of calories the patient usually spends throughout the day. There is therefore no deprivation of necessary calories.

The total caloric requirement for a day is split such that there are three major meals and two to three snacks/day. Calorie-dense foods are avoided. Complex carbohydrates are preferred as is lean meat. It is better to avoid red meat to reduce cardiometabolic risk.

Carbohydrates, proteins, and fat eaten in the correct proportion with limitation of total calories only may be as effective as a low-carbohydrate, high-protein diet or vice versa. Increased consumption of carbohydrates can cause increase in triglycerides and increased consumption of proteins may increase satiety. But otherwise there is nothing to choose between these diets unless in special circumstances.[1]

Food exchanges are used so that the patient has the option of choosing from a variety of food stuffs and is not bored.

The entire meal plan is formulated to be practical, filling, and attractive.

Fad diets and fasting are discouraged. Fad diets which involve eating an excess of one food group over the other, extreme dieting for 1 week to lose weight, or adding weight losing herbs or powders are not beneficial and may actually create harm. They are not practicable in the long run. They may even lead to weight gain once the patient comes back to eating normal foods.

Patients should be strongly advised to avoid skipping meals and fasting. Skipping a meal usually leads to unnecessary snacking, usually with calorie-dense food, or leads to increased hunger, which in turn causes the patient to eat more at the next meal. Ultimately this only results in weight gain. Ideally no meal should be skipped. For the same reason, meals should be eaten on time as far as possible.

Since nutrients can be found in many places, a practical meal plan can be made with the food that the patient is already accustomed to culturally. Food which is culturally different or which is not eaten routinely in that region is not necessary to ensure a good diabetic diet. Strictly speaking, there is no such thing as a diabetic diet, only advice on sensible eating for healthy living.[2]

Once the patient learns how to eat and diabetes is well controlled, patient can eat sweets, ice cream, or snacks occasionally. This should be taken as an exception and not as a routine occurrence and the amount eaten should always be modest – nibbling/tasting as opposed to gorging.

So-called fat-free or diabetic snacks are no exception as the total amount of calories per portion may be equivalent or even more than the original version. Also, as the patient may think that they are safe and not exercise the caution they would otherwise use, leading to overeating. A safe method is to check the labels of all proprietary foods for caloric content and eat accordingly.[2]

Critique of Question 2

Correct Response: b

Limiting portion sizes reduces the amount of calories consumed without depriving the patient of any one food group. Junk food/fast food is usually high in calories which are devoid of any other nutrients or fiber so that they are best avoided or eaten infrequently and in small portion sizes.

Clinical Summary for Practice

There is no such thing as a diabetic diet. People with diabetes need to be taught how to eat sensibly and make healthy food choices. Portion size is important rather than restriction of food groups. Diet should be individualized to give all nutrients while also satisfying the patients' appetite and avoiding boredom. Flexibility is very important. Fad diets and special foods are not a requirement to treat diabetes.

Alcohol and other recreational substances

Consumption of alcohol and usage of recreational substances is also a lifestyle choice. Men with diabetes can drink 1–2 drinks per day. Women can take up to 1 drink per day.[3] Alcohol should be taken with food; fried snacks should be avoided. In calculating daily nutrient intake, calories from alcohol should also be included. When alcohol is allowed, potential for non-compliance must be assessed and pattern of drinking must be known. Smokers should be strongly encouraged to quit.

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CHAPTER 5

Food Exchanges

The food exchange system is useful while planning meals. The exchange system allows a lot of flexibility in the menu.

Purpose of Exchange Systems

The purpose of exchange is to allow a patient to vary the foods eaten from day to day and still consume a constant number of calories with relatively fixed distribution of calories among carbohydrates, protein, and fat, and fixed distribution of calories among the meals. Foods can be grouped into cereals, pulses, green leafy vegetables, other vegetables, fruits, meat, egg, fish, fat, milk, and milk products.

One unit or portion of these food groups provides the following:

S. no.	Food groups	Quantity	Calories	Carbohydrates	Protein	Fat
1.	Cereals	20 g	70	15	2	–
2.	Pulses	20 g	60	10	5	–
3.	Vegetables	80 g	28	5	2	–
4.	Fruits	1 no.	40	10	–	–
5.	Lean meat	50 g	55	–	7	3
	Medium fat meat	40 g	75	–	7	5
	High fat meat	30 g	100	–	7	8
6.	Milk	100 mL	65	5	3.3	3.2
7.	Fat	5 g	45	–	–	5

The information provided below is from IIT Kanpur's website accessed on December 2012 (http://www.iitk.ac.in/hc/foodexchangelist.html).

List 1. Cereal exchange			
30 g provides: Carbohydrate 20 g, Protein 2 g			
Cereals	**Household measures**	**Weight/volume**	**Calories**
Rice		30 g uncooked	100
Wheat flour		30 g uncooked	100
Dalia	1/2 katori cooked	30 g uncooked	100
Sago		30 g uncooked	100
White flour		30 g uncooked	100
Bread	2 slices	40 g	100
Chapati	1.5 (approx. 5–6" diameter)	44 g	100
Jowar roti	0.5	55 g	100
Ragi		30 g uncooked	100
Rice flakes	1 katori	30 g uncooked	100
Oat meal		30 g uncooked	100
Vermicelli	1/2 katori cooked	30 g uncooked	100
Corn flakes		30 g uncooked	100
Maize dry		30 g uncooked	100
Marie biscuit	8 no.		100
Monaco biscuit	4 no.		100
Idlis	2 no.		100
Poha	1/2 katori		100
Upma	1/2 katori		100
Dosa ordinary			120

List 2. Fat exchange			
50 g Calories; Fat 5.5 g			
Fats	**Household measures**	**Weight (g)**	**Calories**
Butter	1½ teaspoon	7.5	50
Ghee	1 teaspoon	5.5	50
Hydrogenated fat (vanaspati)	1 teaspoon	5.5	50
Oil (coconut, mustard sunflower, corn, groundnut, cotton seed, til, palm)	1 teaspoon	5.5	50
Cashew nuts		10	50
Groundnuts, roasted		10	50
Walnuts		7.5	50
Pistachio		7.5	50
Almonds		7.5	50

List 3. Milk and milk products			
50 Calories; Protein 2.5 g			
Milk and milk products	**Household measures**	**Weight/ volume**	**Calories**
Curd	2/3 glass	105 g	50
Butter milk	3 glasses	375 mL	50
Cheese	1 ice cube	15 g	50
Milk (buffalo)	1/3 glass	45 mL	50
Milk (cow)	2/3 glass	90 mL	50
Milk, skimmed*	1 glass	130 mL	50
Milk, skimmed, powder*		15 g	50
Coffee Nescafe + 75 mL milk (without sugar)			50
Tea + 75 mL milk			50
Khoya		15 g	50
1 medium glass 150 mL			
*provides 5 g protein			

List 4. Vegetable exchange			
50 Calories; Carbohydrate 10 g			
Vegetables	**Household measures**	**Weight**	**Calories**
Beetroot (chukander)		75 g	50
Carrot	1–2 no.	105 g	50
Colocasia (arbi)		45 g	50
Onion (big)	1 no.	90 g	50
Onion (small)	2 no.	75 g	50
Potato	1/2 no.	45 g	50
Sweet potato		30 g	50
Tapioca		30 g	50
Yam (zimikand)		45 g	50
Broad beans		90 g	50
Cluster beans		90 g	50
Double beans		50 g	50
Jack, tender		105 g	50
Jackfruit seeds		30 g	50
Leeks		60 g	50
Peas		45 g	50
Singhara		45 g	50
Sambar	1/4 katori	35 mL	50
Cooked vegetable	1/2 katori		50

List 5. Fruit exchange			
50 Calories; Carbohydrate 10 g			
Fruits	**Size/no.**	**Weight (mL)**	**Calories**
Apple	1 small	75	50
Amla	20 medium	90	50
Banana	1/4 medium	30	50
Cashew fruit	2 medium	90	50
Custard apple	¼	50	50
Dates	3	30	50
Figs	6 medium	135	50

Grapes	20	105	50
Grape fruit	1/2 big	150	50
Jack fruit	3 medium pieces	60	50
Mango	1 small	90	50
Melon	1/4 medium	270	50
Orange	1 small	90	50
Lemon	1 medium	90	50
Papaya	2 medium	120	50
Peach	1 medium	135	50
Pear	1 medium	90	50
Plums	4 medium	120	50
Pineapple	1 1/2 slices (round)	90	50
Strawberry	40	105	50
Sweet lime	1 medium	150	50
Tomato	4 medium	240	50
Watermelon	1/4 small	175	50

List 6. Legume and pulse exchange

30 g provides: Carbohydrate 15 g, Protein 6 g

Pulse (uncooked)	**Household measures**	**Weight (g)**	**Calories**
Bengal gram	3/4 katori cooked	30	100
Bengal gram, roasted		30	100
Bengal gram-flour (Besan)		30	100
Cow gram	1 katori cooked	30	100
Horse gram		30	100
White gram (kabuli chana)		30	100
Lentils	3/4 katori cooked	30	100
Moth beans		30	100
Peas, dried	1 katori cooked	30	100
Rajma (kidney beans)	3/4 katori cooked	60	100
Red gram	3/4 katori cooked	30	100
1 katori (volume 150 mL)			

List 7. Flesh food exchange			
70 Calories; Protein 10 g			
Flesh foods	**Household measures**	**Weight (g)**	**Calories**
Egg (hen)	2 no.		100
Fish	1 piece	60	70
Sheep (liver)		60	70
Mutton (muscle)	3 piece	60	100
Pork	1 slice	60	70
Prawn	5–7 pieces	60	70
Chicken	1 breast	60	70
Crab	120 g		70
Beef	1 slice	60	70

List 8. Vegetable exchange			
These vegetables may be used as desired. Carbohydrates and calories are negligible.			
Leafy vegetables		**Other vegetables**	
	Curry leaves	Brinjal	Bitter gourd (karela)
Amaranth	Fenugreek leaves	Cauliflower	Onion stalks
Brussels sprouts	Mint	Drumstick	Pumpkin
Cabbage	Spinach	French beans	Tinda
Coriander leaves		Mango (green)	Tomato (green)

Drinks			
	Household measures	**Volume**	**Calories**
Orange juice	1 big glass	200 mL	30
Tomato juice	1 big glass	200 mL	30
Apple juice	1 big glass	200 mL	100
Grape juice	1 big glass	200 mL	80
Mango juice	1 big glass	200 mL	150

Fast food			
	Household measures	**Volume**	**Calories**
Soft drink	1 bottle	300 mL	120–135
Potato wafers		50 g	430
Samosa	1	40 g	130
Vegetable cutlet	1	100 g	140
Vada	1		150

Cakes and pastries		
	Weight/volume	**Calories**
Plain cake	50 g	150
Chocolate cake	50 g	250
Sponge cake	50 g	150
Pastry	50 g	250–400

Desserts			
	Household measures	**Weight/volume**	**Calories**
Custard		150 g	360
Fruit salad		150 g	150
Fruit salad with cream		150 g	300
Ice cream		150 g	380
Carrot halwa	1 medium katori	100 g	600
Badami halwa		100 g	570

Sweets			
	Household measures	**Weight/volume**	**Calories**
Coconut burfi		25 g	110
Gulab jamun		25 g	200
Laddoo		30 g	160
Rasgulla		150 g	140
Jam	2 tablespoon		80
Honey	2 tablespoon		48

Beverages		
	Volume	**Calories**
Beer	150 mL	65
Wine dry	30 mL	30
Wine dessert	30 mL	40
Whisky, brandy, gin, rum	30 mL	65
Vodka	30 mL	65
Ginger ale	30 mL	9

Sample Exchange List According to the Regions in India

This sample menu provides a diet plan based on calorie consumption per day. With the help of these sample menus, you can plan your meals. The sample menus are based on the principle of food exchanges, for example, cereal exchange, vegetable exchange, fat exchange, etc. Each exchange list has various food items of approximately same calorific value. Thus, one item of a particular exchange list can be substituted for any other item in the same list.

	East	West
Prebreakfast		
List 3	1 tea without sugar	1 coffee or tea without sugar
List 1	4 Marie and 2 Monaco biscuits	4 Marie and 2 Monaco biscuits
List 5	1 small orange	1 apple
Breakfast		
List 1	4 slices of bread	4 slices of bread
List 2	1 teaspoon butter	1 teaspoon butter
List 3	1 glass skimmed milk	1 glass skimmed milk
List 7 or 1/2 exchange from List 1	2 eggs	2 eggs
Lunch		
List 1	3 katori rice	1 ½ chapatis and 2 katori rice
List 4	1 katori vegetable	1 katori vegetable
List 2	2 teaspoon oil for cooking	2 teaspoon oil for cooking

List 3	2/3 glass curd	2/3 glass curd
List 6	3/4 katori rajma	3/4 katori rajma
List 3	1 tea without sugar	1 coffee or tea without sugar
List 1	4 Marie and 2 Monaco biscuits	4 Marie and 2 Monaco biscuits
List 5	1/2 small orange	1/2 apple
Dinner		
List 1	3 katori rice	1 1/2 chapatis and 2 katori rice
List 4	1 katori vegetable	1 katori vegetable
List 2	1 1/2 teaspoon oil for cooking	1 1/2 teaspoon oil for cooking
List 3	1/3 glass curd	1/3 glass curd
List 7 or 1 exchange from List 6	1 piece fish	1 piece chicken

	North	South
Prebreakfast		
List 3	1 tea without sugar	1 coffee without sugar
List 1	4 Marie and 2 Monaco biscuits	6 banana chips
List 5	1 apple	1 small apple
Breakfast		
List 1	4 slices of bread	4 idlis with chutney
List 2	1 teaspoon butter	1 teaspoon oil for cooking
List 3	1 glass skimmed milk	1 glass skimmed milk
List 7 or 1/2 exchange from List 1	2 eggs	2 eggs
Lunch		
List 1	4 1/2 chapatis	3 katori rice
List 4	1 katori vegetable	1/2 katori sambar
List 2	2 teaspoon oil for cooking	2 teaspoon oil for cooking
List 3	2/3 glass curd	2/3 glass curd
List 6	3/4 katori rajma	3/4 katori Rajma
List 3	1 tea without sugar	1 coffee without sugar
List 1	4 Marie and 2 Monaco biscuits	4 Marie and 2 Monaco biscuits

List 5	1/2 apple	1/2 apple
Dinner		
List 1	3 chapatis + 1 katori rice	1 katori rice + 1 1/2 chapatis
List 4	1 katori vegetable	1 katori vegetable
List 2	1 1/2 teaspoon oil for cooking	1 1/2 teaspoon oil for cooking
List 3	1/3 glass curd	1/3 glass curd
List 7 or 1 exchange from List 6	1 piece chicken	1 piece chicken

CHAPTER 6

Monitoring Diabetes

Krishna G. Seshadri

Section 1. How is Diabetes Monitored?

Question 1

A 42-year-old female teacher, a diabetic since 2 years, comes with complaints of pins and needles sensation of both feet but is otherwise asymptomatic. She is currently taking tablet metformin 1 g 1 b.i.d. and tablet glibenclamide 5 mg 1 q.d. She is not on regular follow-up and her last visit to the doctor was 8 months ago. An HbA_{1C} done 1 week ago is 12.2 mg%. Which one of the following statements represents the correct approach to this patient?

(a) Ophthalmologic examination can begin 5 years after diagnosis.

(b) Creatinine needs to be measured only if there is proteinuria.

(c) Annual lipid measurement is warranted.

(d) No intervention is required as it is unlikely that she will have target organ damage.

(e) Glucose measurements are not required since she has an HbA_{1C}.

Discussion

How should Diabetes be Monitored?

The objective of diabetes management is to prevent the complications of diabetes. Monitoring diabetes is, therefore, a process of vigilance that will allow the physician to ensure the following:

- The complications are detected early, and
- The targets that have been established are met.

This includes monitoring for glycemic control, assessment of blood pressure, lipids, and end-organ damage. Monitoring strategies must be individualized and must take into account the type and severity of diabetes, presence of concomitant comorbidities, and organ damage; it is often influenced by access to healthcare and the socioeconomic status of the patient.

Many physicians prefer to obtain fasting and 2-hour blood glucose at least once a month in all patients with diabetes. Some patients will benefit from self-monitoring of blood glucose (SMBG). This is discussed further in Section 2. Real-time continuous glucose monitoring is an option discussed separately in the chapter on newer technologies. Although guidelines differ, generally, in the nonpregnant state, premeal glucoses of less than 130 mg/dL and 2-hour postmeal glucose less than 180 mg/dL are preferable.

Monitoring glycemic control using an HbA_{1C} test helps in understanding the overall glycemic control of the preceding 8–12 weeks. An HbA_{1C} must be performed at least twice a year in all patients who are well controlled and quarterly in patients whose glycemic control is suboptimal. An A_{1C} of less than 7% is desirable in most patients; tighter targets (<6.5%) are appropriate in patients who are newly diagnosed, have long life expectancy, and who are at lower risk for hypoglycemia; higher A_{1C} (<8%) may be sufficient in patients with comorbidities, micro-, and macrovascular complications.[1] Point of care HbA_{1C} is recently more widely available and utilized by physicians who are comfortable in using this modality to guide treatment changes. HbA_{1C} is not a substitute for routine glucose measurements as it does not measure glycemic variability or hypoglycemia. It is also unreliable in conditions that increase blood cell turnover. Most laboratories provide an estimated average glucose along with A_{1C} measurements. The eAG has been validated in several studies the most extensive being the ADAG.[2]

In addition to monitoring glycemic control, all patients with diabetes must have renal function measured annually. Blood urea nitrogen, creatinine, urine examination for proteinuria, and, if this is normal, measurement of the albumin/creatinine ratio (see Chapter 9, "Prevention of Diabetic Nephropathy") in a spot urine sample is recommended. A urine albumin excretion of >30 mg/24 hours repeated two or three times initially confirms persistent albuminuria. A significant number of patients with type 2 diabetes mellitus (T2DM) may have increased serum creatinine in the absence of increased urinary albumin.[3] Therefore annual serum creatinine levels and estimation of the glomerular filtration rate (eGFR) in all patients with T2DM irrespective of albumin excretion is recommended. eGFR is calculated using the modification of renal diet study (MDRD) equation or the CKD - Epi equation. A convenient online calculator is available at http://www.nkdep.nih.gov.

Cardiovascular risk factors must be assessed in all patients annually. Routine ECG is not recommended but may be obtained based on the discretion of the physician.[1] Many physicians choose to obtain a baseline ECG at the age of 40. There appears to be no benefit to screening patients for CVD in the absence of symptoms and a normal ECG.[4] The effectiveness of newer noninvasive screening tests in T2DM remains undetermined at this time.

A lipid profile must be annually in all patients (see Chapter 14, "Dyslipidemia in Diabetes," for targets). The blood pressure must be measured at every visit. A target of less than 130/80 mmHg is reasonable for most patients.

All patients with T2DM must have a dilated fundus examination at the time of diagnosis and at least once in 2 years thereafter to detect retinopathy. Patients with retinopahty should have annual or more frequent examinations.

A comprehensive foot examination must be performed at least annually. An assessment for neuropathy should be done annually (see Chapter "Diabetic Neuropathy"). This is usually accomplished by testing for touch, warmth, and vibration using a tuning fork. There is no role for routine nerve conduction studies. The patient must be taught to inspect her feet every day. Initial screening for peripheral arterial disease (PAD) should include questioning for claudication and palpation of peripheral pulses. There is a recommendation to perform ankle brachial index (ABI) in all patients over the age of 50 or patients under the age of 50 with risk factors for PAD.

Lifestyle modifications must be assessed at each visit and changes recommended appropriately.

Critique of Question 1

Correct Response: c

A significant number of patients with T2DM have end-organ damage at diagnosis. Hence, screening for eye and renal dysfunction must begin at the diagnosis and periodically thereafter even if they are asymptomatic. Although microalbumin is a reliable indicator of nephropathy, a significant number of patients may have low GFRs in the absence of albuminuria. Creatinine must therefore be measured independently and the eGFR calculated at least annually. A baseline and annual lipid measurement is invaluable and is the correct statement in this question. HbA_{1C} provides an average of blood glucose over the preceding 8–12 weeks; therapeutic decisions must also factor in fasting and postmeal glucose if SMBGs are not performed. A_{1C} complements measures of glycemia and cannot substitute them.

Clinical Summary for Practice

Patients with diabetes require periodic office visits that include a comprehensive examination, including measurement of blood pressure, foot examination, and measurement of key indices including glucose, periodic HbA_{1C}, lipids, and renal function. Periodic referral to an ophthalmologist is crucial. Education must be provided to emphasize the need for monitoring even in the absence of symptoms or target-organ damage.

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Section 2. Self-Monitoring of Blood Glucose

Question 2

A 53-year-old woman has T2DM for 15 years. She was on oral hypoglycemic agents (OHAs) but was switched to insulin 4 months ago. She is currently taking a combination of neutral protamine hagedorn (NPH) and regular insulin twice daily with a small afternoon dose of regular insulin. She is a traveling executive and frequently has delayed lunch. She complains of dizziness at around 10 o'clock in the morning. One week ago, she complained of feeling bizarre but did not have any sweating or palpitations. She is regular with her visits and monitors her sugars in a lab near her house once a week. Her HbA_{1C} is 9.6; BUN is 28, and Cr is 1.7. Which one of the following is the most appropriate for this patient?

(a) Stop insulin and reinstitute OHAs.

(b) Switch to basal insulin and OHAs.

(c) Obtain a glycosylated fructosamine.

(d) Teach the patient to monitor her glucose.

(e) Switch an insulin pump.

Discussion

With a small finger prick and a microliter or less of blood or less, patients with diabetes can know their blood glucose at any time. This allows patients to relate to events in their daily life and treatment regimens to glycemic results. The introduction of SMBG thus caused a shift in the focus of diabetes management from the physician's office to the hands of the patient.[1] With adequate education and communication, SMBG provides patients with a great opportunity to take charge of their condition.

The quality of glucose meters has consistently improved over the years with an accompanying decline in the cost. Most glucose meters use glucose strips impregnated with glucose oxidase, glucose dehydrogenase, or hexokinase to convert blood glucose into gluconic acid and hydrogen peroxide when a drop of blood is added to it. This reaction is then quantified by colorimetric methods.[2]

Accuracy standards have been established; many meters meet these requirements. Glucose meters, however, are generally less reliable in extremes of glycemic ranges. Low hematocrits increase SMBG results.[3] Operator-related errors are more significant than instrument-related errors and include failure to calibrate, improper use of control solutions, poor hand washing, and improper storage.[4] Patient education significantly reduces these errors.

The use and acceptance of SMBG has increased in clinical care; it, however, adds considerably to the cost of care and therefore must be chosen judiciously. In a systematic review of use of SMBG in patients who do not use insulin, a 0.39% improvement in HbA_{1C} was seen. It is important to note that many of the studies that were included in this analysis included other measures that are associated with improved outcomes, especially education. Although the results translate to a 14% decrease in complications, the general view appears to be that SMBG is not indispensible in patients with T2DM who are not on insulin.[5] Although in the motivated patient and in combination with appropriate physician feedback, it can be an excellent educational tool, the cost–benefit ratio does not justify its use in resource-limited situations. Several studies support this view.[6]

In patients who require insulin, SMBG is more useful in preventing hyperglycemia and hypoglycemia. It is especially invaluable in insulin-requiring patients with hypoglycemia unawareness and in the pregnant diabetic. The number of glucose measurements and the periodicity in T2DM is unclear and must be individualized based on patient parameters, preference, compliance, and motivation. A staggered chart that measures glucoses one or at the most two times a day but done at different times of the day over a period of time can be used in lieu of cumbersome multiple measurements. When supplemented by office-based glucose measurements and HbA_{1C}, these can provide a valuable tool to allow both physician and patients to adjust lifestyle and medications appropriately.

It is important for physicians to evaluate each patient's monitoring technique, both initially and at regular intervals thereafter. In addition, optimal use of SMBG requires proper interpretation of the data. Patients should be taught how to use the data to adjust food intake, exercise, or pharmacological therapy to achieve specific glycemic goals, and these skills should be re-evaluated periodically. It is also important for physicians to review SMBG data with patients as often patients may not take action on either low or high values.[7]

Continuous glucose monitoring is also available. It is of limited value in patients who are on OHAs alone or on OHAs with a stable dose of insulin. It is more useful in patients with brittle diabetes and may be valuable in patients with hypoglycemia unawareness.[8]

Critique of Question 2

Correct Response: d

The patient's glycemic control is poor. Reinstituting OHAs will not help this patient. Basal insulin does reduce the incidence of nocturnal hypoglycemia and severity of hypoglycemia; in this patient, the key issue is the need to educate her about the relationship between glucose and meals. In addition, she has hypoglycemia unawareness which will lead to dangerous hypoglycemia, from which she may not recover. Introduction of SMBG with education on how to respond to high and low glucose is the most appropriate intervention for this patient. Fructosamine will not add any more information and is a fairly unreliable test. An insulin pump is an option in selected patients; this patient will benefit most from SMBG.

Clinical Summary for Practice

Self-monitoring of blood glucose provides patients with an opportunity to take charge of their diabetes. It is of limited value in patients who are on OHAs. Patients who require multiple doses of insulin or have recurrent hypoglycemia and/or hypoglycemia unawareness benefit the most from SMBG. Appropriate education, review, and follow up are the keys to success of SMBG.

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Practice Box

1. Measure BP and examine foot at every visit.
2. If SMBG is not done, measure FPG and 2-h PP monthly.
3. Measure HbA_{1C} in patients with stable diabetes twice a year; quarterly in patients with poor control.
4. Measure lipids annually.
5. Check for neuropathy and for peripheral vascular disease at least annually.
6. Obtain BUN, creatinine, and urine microalbumin annually.
7. Refer to an ophthalmologist annually initially and if there is no retinopathy at least once in 2 years.
8. Consider SMBG in patients on multiple doses of insulin or with recurrent hypoglycemia or hypoglycemia unawareness.
9. Review SMBG records and SMBG technique at each visit and educate patient on LSM and dose changes based on the values.

CHAPTER 7

Pharmacologic Therapy for Glycemic Control: Oral Hypoglycemic Agents

Manoj D Chadha

Section 1: Factors before Choosing an Anti-Diabetic Agent

Question 1

A 55-year-old man, regional technology salesman, diagnosed with type 2 diabetes mellitus (T2DM) approximately 12 months ago. He rarely exercises and has difficulty following a well-balanced diet because he travels so much. In addition to T2DM, he has a history of dyslipidemia and chronic back pain. His current medication regimen includes metformin 1000 mg twice daily for his T2DM, atorvastatin 40 mg once daily for dyslipidemia, and ibuprofen 800 mg as needed for back pain.

Physical examination revealed that he is obese (body mass index [BMI], 31.0 kg/m^2) with mildly elevated blood pressure (142/90 mmHg); other findings were normal. Laboratory findings were normal, except for mildly reduced kidney function (estimated glomerular filtration rate [eGFR] 79 mL/min/1.73 m^2) without microalbuminuria (urine albumin–creatinine ratio ≤10 mg/g) and an elevated glycated hemoglobin (HbA_{1C}) of 8.0%.

What additional information would be most important prior to determining the change in antihyperglycemic therapy?

(a) Ethnicity

(b) Family history of T2DM and cardiovascular disease (CVD)

(c) Marital status

(d) Preference for drugs with a certain route of administration

Discussion

T2DM is a progressive and complex disease characterized by deterioration of glycemia and concomitant comorbidities.[1] The United Kingdom Prospective Diabetes Study and other pivotal trials have demonstrated a consistent link between glycemic control and complications in T2DM – good glycemic control is the cornerstone of the management of diabetes.[2,3]

The goals for managing patients with T2DM are different; hence the concept of individualized T2DM management has become a useful and popular theme of treatment. In 2012, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) published a position statement, *Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach*, which illustrates this approach.[4]

In addition to clinical trial data, it is important to consider the following factors while choosing an antidiabetic agent:

- The duration of diabetes
- HbA_{1C} reduction required and the ability of the drug to provide that reduction
- The durability of the drug
- The ability of the drug to address the pathophysiology of the disease
- The ability to address the components (fasting and postprandial) of glycemia
- The ability to minimize hypoglycemia and weight gain
- Safety in variety of clinical situations including cardiovascular safety
- Adverse events associated with the drug
- Cost effectiveness of therapy
- Route of medication delivery (oral or injectable) preferred by the patient

Oral hypoglycemic agents are the most commonly prescribed pharmacotherapeutic agent in T2DM.

Table 1 summarizes the factors that influence the choice of drugs.

The ultimate goals of hyperglycemia management are to (i) avoid acute symptoms of hyperglycemia and hypoglycemia; (ii) avoid instability in blood glucose over time; and (iii) prevent or delay the development of diabetes complications without adversely affecting quality of life.[4]

Different professional organizations suggest the use of different HbA_{1C} targets; however what appears to be prudent based on evidence is that for the majority of

Table 1. Factors influencing the choice of drugs

Criteria	Most favorable	Neutral	Least favorable
Durability	Thiazolidinediones	Metformin	? Sulfonylurea
Hypoglycemia	Metformin, DPPIV inhibitors, GLP-1 agonists, bromocriptine SGLT2 inhibitors	AGI, thiazolidinediones	Sulfonylurea Insulin
Weight gain	Metformin, GLP-1 agonists SGLT2 inhibitors	AGI, DPP-IV inhibitors	Sulfonylurea Insulin Thiazolidinediones

patients, an HbA_{1C} <7% is reasonable. In a subset of patient with no comorbidity and short duration of diabetes, a more aggressive target of <6.5 is desirable if it can be achieved without running the risk of hypoglycemia. Similarly for those with comorbidities (including CVD), long duration of diabetes, recurrent hypoglycemias, a higher HbA_{1C} is more acceptable.[5]

Oral hypoglycemic agents differ considerably in their mechanism of action. The sulfonylureas, which have been the sheet anchor of therapy for many years, mainly increase the amount of insulin secreted by the pancreas. Through a different mechanism of action involving glucagon-like peptide-1 (GLP-1), the incretin mimetics and dipeptidyl peptidase-IV (DPP-IV) inhibitors achieve the same thing. The mechanism of action of metformin is largely unknown but among the other things is known to decrease hepatic glucose output and reduce insulin resistance. The thiazolidinediones decrease insulin resistance as their principal mechanism of action. Alpha glucosidase inhibitors (AGIs) delay the absorption of complex carbohydrates and are principally useful in postprandial hyperglycemia. SGLT2 inhibitors increase glucose excretion. Immediate-release bromocriptine works through a central mechanism that is not very clear. A review of OHA classes is presented in Box 1.

HbA_{1C} reductions achieved with the most OHAs and with combination are summarized in Tables 2 and 3, respectively. At higher HbA_{1C}, the OHA achieves a greater HbA_{1C} reduction. At the highest HbA_{1C}, the majority of the contribution to the HbA_{1C} is from fasting plasma glucose (FPG); at lower HbA_{1C}, there is higher contribution from postprandial plasma glucose. Thus at higher HbA_{1C}, primary target is FPG. At lower HbA_{1C}, therapy may be better directed at the predominant abnormality that is evident on glucose profile.

Box 1. A review of OHA classes

Metformin

Metformin decreases hepatic glucose output and improves insulin resistance through as yet unelucidated mechanisms. The starting dose of metformin is 500 mg once a day, gradually titrated upward to maximum of 2000 mg/day in divided doses. With long-term use, 0.82% reduction of HbA_{1C} is seen with metformin use. Some studies have suggested that metformin causes modest weight loss and improvement in dyslipidemia. The exact mechanism of weight loss is not known, but it is suggested that it decreases calorie intake and has weak DPP-IV inhibitory activity, thereby enhancing the incretin effect or prolonging the suppression of ghrelin.

Gastrointestinal (GI) side effects can be minimized by starting at a low dose or using sustained-release preparations. A recent Cochrane systematic review demonstrated no increased association of lactic acidosis with metformin as compared to placebo. Metformin is contraindicated in patients with renal dysfunction (serum creatinine >1.4 mg/dL in females and 1.5 mg/dL in males or creatinine clearance <30 mL/min).

Thiazolidinediones

Thiazolidinediones improve insulin sensitivity and promote differentiation of fat cells through their action on peroxisome proliferator receptor-gamma (PPAR-γ). These drugs act to sensitize tissues such as adipose tissue and muscle to insulin via a range of effects that include a reduction in circulating nonesterified fatty acids and alteration in expression of adipocytokines such as TNF-α, leptin, and adiponectin that may influence insulin sensitivity. HbA_{1C} reduction with pioglitazone is in the range of 0.6–1.9%.

Pioglitazone 45 mg increased HDL by 19%, increased LDL by 6%, and decreased triglycerides by 9.3% after 26 weeks' therapy. PIOPOD, PROACTIVE trials have shown cardiovascular benefits of this drug.

Pioglitazone is associated with dose- and time-dependent weight gain. The average weight gained ranged from 0.3 to 0.5 kg in patients treated with the drug. When combined with sulfonylureas or insulin, the weight gain was more dramatic. Mechanism for weight gain includes increased adipogenesis resulting from PPAR-γ activation, fluid retention, and increased appetite. With thiazolidinediones, these is an increase in subcutaneous fat whereas reduction in visceral fat. This change in ratio of visceral to subcutaneous fat seems to underlie the improvement in glycemic control despite an overall increase in body weight. Anemia was reported in 1% of patients, mostly an effect of hemodilution. Pioglitazone is associated with increased incidence of macular edema and wrist fractures.

Recently, a controversy has been raised of an apparent risk of bladder cancer in patients on pioglitazone. AFSSAPS the French regulatory authority followed by Germany on June 9, 2011 suspended the use of pioglitazone-containing products for the treatment of T2DM in France on the basis of a small increased risk with statistical significance of bladder cancer. In July 2011 after finalizing its review, the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) confirmed that these medicines remain a valid treatment option for certain patients with T2DM but that there is a small increased risk of bladder cancer in patients taking these medicines. They concluded that the small increased risk can be reduced by appropriate patient selection and exclusion along with periodic review including efficacy and safety. The major correlation between pioglitazone and bladder cancer is the *duration of therapy > 24 months* and *cumulative dose of > 28,000 mg*, which means that the average daily dose of pioglitazone is about 40 mg/day. In India, we generally do not use doses greater than 15 mg, which means to achieve a cumulative dose of 28,000 mg we would take 5 years and if we use 7.5 mg it would take 10 years.[6] In June 2013, the Indian government suspended pioglitazone over safety concerns, only to revoke the suspension a little over a month later with a safety warning of increased risk of bladder cancer. US FDA recommends avoiding use of pioglitazone in patients with active bladder cancer and with caution in patients with a prior history of bladder cancer. Also patients should be counseled to report any signs or symptoms of blood in the urine, urinary urgency, pain on urination, or back or abdominal pain, as these may be due to bladder cancer.[6]

Rosiglitazone, another drug from the same group, has been withdrawn from most of the markets in lieu of significant increases in congestive heart failure and ischemic cardiovascular events.

Alpha-glucosidase inhibitors

When taken with food, acarbose reduces postprandial glucose peak by inhibiting the digestive enzyme, alpha glucosidase, which normally breaks carbohydrates into their monosaccharides. Some improvement in lipids has been reported. Undigested carbohydrates then pass into the large intestine where bacteria metabolize them, which may explain the

common side effects of postprandial fullness/bloating, abdominal pain, flatulence, and diarrhea. In UKPDS, adding acarbose to other therapies resulted in further 0.5% drop in HbA_{1C}. The effect of AGIs on body weight is controversial. The ESSEN[5] study showed that acarbose was weight-neutral after 24 weeks of intervention. Later, in ESSEN II[7] study, acarbose induced 0.8 kg weight loss over 24 weeks of treatment. In recent meta-analysis, acarbose was found to decrease BMI.

Incretin-based therapy

The incretin mimetics potentiate the insulin secretory response to oral glucose and suppress glucagon release.

GLP-1 analogs

The naturally produced GLP-1 cannot be used therapeutically as they get degraded by serum proteases predominantly DPP-IV. Novel methods have been developed to augment its half-life, such that its anti-hyperglycemic effects can be exploited. They can broadly be classified as exendin-based therapies (exenatide, exenatide once weekly), DPP-IV-resistant analogues (lixisenatide, albiglutide), and analogues of human GLP-1 (liraglutide, taspoglutide). Currently, commercially available analogues are exenatide, exenatide once weekly, and liraglutide. Taspoglutide was withdrawn from market in view of hypersensitivity reactions. HbA_{1C} reduction is to the tune of -0.8% to 1.5% with 0.33% greater reduction with liraglutide compared with exenatide. GLP-1 analogs reduce both fasting and postprandial glycemia.[8]

The GI side effects are most pronounced with exenatide BID (nausea 28%, vomiting 9.9%) compared to liraglutide (nausea 25.5%, vomiting 6.0%). Liraglutide is less immunogenic than exenatide, and fewer than 10% of liraglutide-treated patients developed antibodies to liraglutide.[8] GLP-1 agonists should be avoided in patients with past history of pancreatitis. GLP-1 agonists have been shown to cause C-cell hyperplasia of thyroid in rodents. The GLP-1 receptor density is 45 times that of human in rodents. However, GLP-1 analogs should be avoided in patients with medullary thyroid carcinoma (MTC), family history of MTC or MEN2 syndrome.[9]

DPP-IV inhibitors

The orally active DPP-IV inhibitors that prevent breakdown of GLP-1 are sitagliptin, vildagliptin, saxagliptin, and linagliptin. DPP-IV inhibitors reduce postprandial glycemic excursion and, to some extent, also increase basal concentrations of GLP-1, thereby having modest effects on fasting glycemia. In a meta-analysis that included information regarding treatment of T2DM with sitagliptin and vildagliptin for >12 weeks compared with placebo and other oral antidiabetic drugs, Amori *et al.* showed a reduction of 0.74% in HbA_{1C} levels. Thus DPP-IV inhibitors were only slightly less effective than sulfonylureas and as effective as metformin and thiazolidinediones in regard to reducing blood glucose.[10] DPP-IV inhibitors are weight neutral. The three most commonly reported adverse reactions in clinical trials are nasopharyngitis, upper respiratory tract infection, and headache. Increased incidence of pancreatitis has been noted in post-marketing surveillance; however cause–effect relationship is not established.[11] USFDA recommends avoidance in patients with history of pancreatitis.

SAVOR TIMI 53 trial with saxagliptin and EXAMINE trial with alogliptin evaluated cardiovascular safety of DPP-IV inhibitors. These studies found no effect on the risk of fatal or non-fatal cardiac events and no increase in the risk of pancreatitis or pancreatic cancer. These studies were limited by short-term follow up and marginal HbA_{1C} reduction. However, these studies showed that admissions with congestive heart failure were more in patients on DPP-IV inhibitors; however the *p* value was nonsignificant.[12,13]

Pharmacology of various incretins is summarized in Table 4.

Sulfonylureas and glinides (non-sulfonylurea) secretagogues

Insulin secretagogues bind to the sulfonylurea receptors, a subunit of voltage-dependent potassium adenosine triphosphate (K-ATP) channels on the β-cells. Closure of these channels with subsequent inhibition of the efflux of K^+ ions from the resting β-cells causes opening of voltage-dependent calcium channels. The calcium entry into the cells causes contraction of microtubules followed by release of insulin from vesicles. Thus, sulfonylureas induce insulin secretion at lower plasma glucose threshold.

Glinides induce insulin secretion similarly, but they bind to sulfonylurea receptor at a different site. Unlike conventional sulfonylureas, they are not internalized within β-cell and have less stimulatory effect during postabsorptive conditions. Therefore, the risk of severe hypoglycemia is less than that with classical sulfonylurea. They are short acting and target postprandial hyperglycemia.

During sulfonylurea monotherapy, most studies report a reduction in HbA_{1c} of 1–2% compared with placebo. The glucose-lowering effect progresses in proportion to the dose. However, this effect plateaus at 50% of the maximum recommended dose. After good initial response to sulfonylurea therapy, the yearly failure rate is about 5–7%. After 10–12 years, most patients require additional oral medications or insulin therapy.

The main and frequent side effect during therapy with insulin secretagogues is hypoglycemia. Large variation of hypoglycemic attacks has been reported depending upon pharmacological agents used and the metabolic control: from 2% to 38% in the glibenclamide-treated patients of the ADOPT study and the UKPDS. Hypoglycemia, induced by sulfonylurea, is of particular concern in older patients and patients with reduced liver and kidney functions. The incidence of hypoglycemia is more common in first- and second-generation drugs like glibenclamide. Sulfonylurea treatment is associated with weight gain from 2 to 5 kg. In UKPDS, the mean weight ranged from 1.7 kg (glibenclamide) to 2.6 kg (chlorpropamide). The results were confirmed by ADOPT study where body weight increased by 1.6 kg in the first year.

Repaglinide and nateglinide seem to increase body weight only slightly or to be at least weight-neutral. In a 16-week study, repaglinide was associated with 1.8 kg weight gain as compared to 0.7 kg in the nateglinide group.

Sodium glucose cotransporter (SGLT-2) inhibitors

The kidneys are important regulators of glucose homeostasis. In nondiabetics, glucose is only found at trace levels in the urine; approximately 160–180 g glucose is filtered and reabsorbed every day. Two glucose transporter families are involved with glucose reabsorption – the passive glucose transporters (GLUTs) and the active SGLTs. There are two types of SGLTs in the kidney – SGLT1 and SGLT2. SGLT2 is a high-capacity, low-affinity transporter located on the convoluted proximal tubule, which accounts for approximately 90% of glucose reabsorption. SGLT1 is a low-capacity, high-affinity transporter located in the S3 straight segment of the proximal tubule, as well as extensively in the small intestine (where it absorbs glucose and galactose), and accounts for approximately 10% of glucose reabsorption in the kidney.[13]

Once glucose serum concentrations increase above the maximum reabsorption capacity, referred to as the *renal threshold*, the excess glucose is excreted in the urine (glucosuria). In patients with T2DM, the reabsorption of glucose is increased, and there is evidence of upregulation of SGLT2 in the proximal tubules. Thus, in the hyperglycemic state found in T2DM, the kidneys retain more glucose than is physiologically needed. SGLT2 inhibitors reduce the renal threshold for reabsorption of glucose that has been filtered by the kidneys, resulting in excretion of this excess glucose in the urine. The amount of filtered glucose is dependent on the blood glucose concentration and renal function.[13]

Two SGLT2 inhibitors currently approved are *dapagliflozin and canagliflozin*. Other advantages are weight loss and reduction in blood pressure. SGLT2 inhibitors cause caloric loss by decreasing absorption of glucose in the kidney and causing excretion of glucose in the urine thereby causing weight loss. Body weight reductions of approximately 1–3 kg are observed with SGLT2 inhibitor treatment.

Overall, the most commonly reported adverse events of SGLT2 inhibitors are urinary and genital tract infections, resulting from increased glucose excretion, which provides a favorable growth environment for otherwise commensal microorganisms. SGLT2 inhibitors can also cause osmotic diuresis, which can result in postural hypotensive episodes and dizziness; however, these adverse events are uncommon. The long-term cardiovascular safety needs to be determined.[13]

Table 2. HbA_{1C} reductions with OHAs	
Drug	**HbA_{1C} Reduction**
Metformin	1.14
Sulponylureas	1.52
Repaglinide	1.32
Nateglinide	0.54
Pioglitazone	0.97
AGIs	0.77
Gliptins	0.8
GLP-1 analogs	0.6% to -1.5%
SGLT2 inhibitors	0.62% to 1.0%
Bromocriptine	

Table 3. HbA_{1C} reductions with combination therapy	
Combination	**HbA_{1C} reduction**
Sulfonylurea + metformin	1.7
Sulfonylurea + pioglitazone	1.2
Sulfonylurea + acarbose	1.3
Pioglitazone + metformin	0.7
DPP-IV inhibitor + metformin	0.7
DPP-IV inhibitor + pioglitazone	0.7

Table 4. Features of incretin-related therapy				
	Administration/Dose	**Clearance**	**Side effects**	
GLP1 receptor agonist	Subcutaneous		Weight loss	Gastrointestinal
Exenatide	5–10 µg twice a day, 2 mg once a week	Renal	+	++
Liraglutide	0.6–1.8mg once a day	Extrarenal	+	+
DPP-IV inhibitor	Oral		⇒	⇒
Sitagliptin	100 mg OD	Renal	⇒	⇒
Vildagliptin	50 mg twice a day	Renal	⇒	⇒
Saxagliptin	5 mg once a day	Renal	⇒	⇒
Linagliptin	5 mg once a day	Extrarenal	⇒	⇒
Alogliptin	Oral	Renal	⇒	⇒

Exenatide once a week has less GI side effects.

The ability of an OHA to sustain its action without the need for additional drug is called durability. The durability of a drug is an indirect measure of its ability to preserve β-cell function. Of the drugs evaluated, the sulfonylureas appear to have worst durability, glitazones the best, with metformin being intermediate. There are no data on the durability of GLP-1 agonists or DPP-IV inhibitors. Their mechanism of action, though, appears to suggest that they may have a favorable effect.[7]

Hypoglycemia is a significant concern with glycemic control and is often the limiting factor in achieving glycemic targets. Sulfonylureas have the maximum risk of hypoglycemia. The risk is minimal with metformin, incretin therapy, pioglitazone, AGIs, and SGLT2 inhibitors.

Weight gain is an important concern in patients who are on diabetes therapies. In the UKPDS for instance, for every 1% reduction in HbA_{1C}, a 4-kg weight gain was also observed. Metformin, SGLT-2 inhibitors, and the GLP-1 agonists reduce weight, the later significantly more so. The DPP-IV inhibitors and the AGIs are weight-neutral. Sulfonylureas and the glitazone promote weight gain.

The thiazolidinedione rosiglitazone was the first drug to be pulled off in lieu of lack of cardiovascular safety. Metformin and pioglitazone appear to have a higher degree of cardiovascular safety than sulfonylureas. Newer generation sulfonylureas appear to be slightly better than traditional sulfonylureas. Bromocriptine IR was the first drug to get FDA nod after establishing cardiovascular safety. Incretin mimetics have pleiotropic effects which may be beneficial in atherosclerosis; however EXAMINE and SAVOR-TIMI trials using DPP-IV inhibitors do not show this. Large-scale randomized, prospective, clinical studies and their subanalysis will provide the evidence whether incretin therapy provides clinical benefits of vascular protection beyond glycemic control.

Pioglitazone should be avoided in those with history of bladder carcinoma. Similarly incretins should be avoided in those with pancreatic cancer, pancreatitis, and medullary thyroid carcinoma.

The safety of a drug in various comorbid conditions influences choice (Table 5). Metformin and sulfonylureas are limited by renal failure. GLP-1 agonists and DPP-IV inhibitors with reduced dose are safe in stage 3–4 CKD. SGLT2 inhibitors are safe to use in T2DM patients with mild renal dysfunction. SGLT2 inhibitors should not be initiated in T2DM patients with moderate to severe renal dysfunction (eGFR<60 mL/min/1.73 m^2). There is limited experience in clinical trials in patients with hepatic impairment for SGLT2 inhibitors. No dosage adjustment is necessary for patients

Table 5. Comorbid conditions that influence the choice of therapy

Comorbidity	Preferred	Against
Renal failure	Insulin Gliptins Repaglinide	Sulfonylureas Metformin SGLT2 inhibitors
Hepatic disease	Insulin	Metformin AGI Thiazolidinediones
Coronary artery disease	Insulin GLP-1 agonist	Thiazolidinediones Glibenclamide

with mild or moderate hepatic impairment. Thiazolidinediones are contraindicated in hepatic dysfunction. Patients with coexistent cirrhosis or GI diseases are poor candidates for AGIs.

Cost is an important consideration in treatment. Metformin is usually the first-line treatment. Various second-line agents like sulfonylureas, AGIs, thiazolidinediones, DPP-IV inhibitors, GLP-1 agonists, SGLT-2 inhibitors, and bromocriptine IR are available. There are no guidelines to recommend preferential use for any of these agents. The decision should be individualized depending on special patient characteristics. Several professional societies have suggested varied approaches to choice of agents. The American Diabetic Association (ADA)[5] takes a stepped care approach starting with metformin and an emphasis on early insulin use.

The American Association of Clinical Endocrinologists (AACE)[15] choose a more real-world HbA_{1C}-based approach with a broad choice of agents, an aggressive early double or triple combination. Patients with HbA_{1C} of between 6.5% and 7.5% may be offered metformin, a thiazolidinedione, DPP-IV inhibitor, AGI, or nonsulfonylurea secretagogue.

Almost all professional bodies support metformin, by virtue of its long track record of safety, salutary effects in weight loss, and other benefits; the other agents are reserved for situations where metformin is not tolerated.

When monotherapy fails, other agents are added. As a rule, the first drug is never discontinued. A second drug is added unless there is clear intolerance or incompatibility of the combination. The choice of the second drug depends again on the HbA_{1C} reduction required, the predominant glycemic defect that must be

Table 6. Comparison of initial therapies in various guidelines

Category	ADA	AACE	NICE
Initial therapy	Metformin	Metformin AGI Thiazolidinediones DPP-IV	Metformin Sulfonylurea
Differentiator for initial therapy	None	HbA_{1C}	None Provides use of sulfonylurea at higher HbA_{1C}
Dual therapy	Not recommended	Recommended	Not recommended
Triple therapy	Not recommended	Recommended	Not recommended

ADA, American Diabetic Association; AACE, American Association of Clinical Endocrinologist; NICE, National Institute for Centre of Excellence.

addressed, and comorbidities. ADA also offers the option of adding basal insulin. Initial therapies in various guidelines have been compared in Table 6.

Critique of Question 1

Correct Response: d

In general, all these factors can be considered and used to make treatment decisions; however, the patient's preference for drugs with a certain route of administration would provide the most value, as this could potentially eliminate certain treatment options. While sensitivity to patients' ethnicity can be helpful with lifestyle decisions, antihyperglycemic agents do not demonstrate differences in efficacy or safety/tolerability based on ethnicity. Family history of T2DM and CVD can provide perspective regarding patients' cardiovascular (CV) risk, but, to date, none are of greater value when setting patients' glycemic antihyperglycemic agents. Marital status may provide some insight into patient's attitude, treatment efforts, and support system.

Clinical Summary for Practice

The choice of an agent largely depends on the following:

- The duration of diabetes
- HbA_{1C} reduction required and the ability of the drug to provide that reduction
- The durability of the drug
- The ability of the drug to address the pathophysiology of the disease
- The ability to address the components (fasting and postprandial) of glycemia
- The ability to minimize hypoglycemia and weight gain
- Safety in variety of clinical situations including cardiovascular safety
- Adverse events associated with the drug
- Cost-effectiveness of therapy
- Route of medication delivery (oral or injectable) preferred by the patient

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Section 2. Initial Combination Therapy

Question 2

A 57-year-old man presents with T2DM. He went for a routine check-up suggested by his office. He has a history of snoring with frequent waking up in the middle of the night and daytime fatigue. His father has diabetes. Physical examination reveals the following: BMI 32 kg/m^2; BP 140/80 mmHg; FBS 200 mg/dL; 2 hr PP 260 mg/dL; HbA_{1C} 8.6%; BUN 22 mg/dL; Cr 1.2 mg/dL; total cholesterol 190 mg/dL; TGL 160 mg/dL; HDL 40 mg/dL. In addition to lifestyle changes, which one of the following is the most appropriate next step?

(a) Start metformin 500 mg OD titrating to 2000 mg/day
(b) Start sitagliptin/metformin combination (50/1000 mg) twice a day
(c) Start liraglutide 0.6 mg titrating to 1.2 mg sc with metformin
(d) Start pioglitazone 15 mg + metformin 1 g daily
(e) Start glimeperide 2 mg + metformin 1 g daily

Discussion

There has been a paradigm shift in the management of patients who present with higher HbA_{1C}. Data from pivotal trials suggest that the benefits of glycemic control are predominantly seen when HbA_{1C} are aggressively reduced early in the course of disease. There is little benefit or even harm when the proverbial barn door is closed after the horse has bolted. In addition, there appears to be legacy effect (also known as metabolic memory) through which early aggressive reductions result in accrued benefits later.[1] Although some experts advocate early insulin as a solution, real-life practice scenarios make this recommendation difficult to implement. Early use of combination therapy, including double or triple drug combinations, if required on the go, has emerged as an important option. Although the evidence to support combinations is meager, real-life practice supports the wisdom, acceptability, and relative safety of such a choice. Guidelines issued by the AACE support initial and add-on combination including triple combinations, if needed. In each of these situations, the other fundamental issues outlined in Section 1 and the properties of the drugs must guide the choice of therapy. When patients have HbA_{1C} between 7.5% and 9.0%, AACE recommends double combinations. As the HbA_{1C} gets closer

to 9%, given the magnitude of reduction required, a sulfonylurea is usually required. When this fails, a third agent or basal insulin may be added. When patients present with HbA_{1C}>9% and are asymptomatic, a trial of three drugs (one of which is sulfonylurea) is tried failing which insulin is added. Symptomatic patients with HbA_{1C} >9% are best started on insulin either alone or in combination with OHAs. It must be remembered that at any of the higher HbA_{1C}, insulin is an important option for the compliant and motivated patient. Insulin therapy is detailed in Chapter 8.

Critique of Question 2

Correct Response: c

Metformin monotherapy is not sufficient to reduce HbA_{1C} to desirable levels in the patient. Although glimeperide in combination will reduce HbA_{1C} significantly and can be titrated up by another 2 mg if required, any weight gain in this patient who has obesity with suggestion of obstructive sleep apnea would be undesirable. Pioglitazone similarly carries the risk of weight gain. The addition of metformin does not significantly offset weight gain. Gliptins are weight-neutral; however, when combined with metformin, modest weight loss is seen mostly attributable to metformin. Liraglutide, however, produces significant sustained weight loss and in this patient, would be ideal agent in combination with metformin. Nausea is significant with liraglutide, but usually reduces or disappears after prolonged use. In addition to GLP-1 agonists, this patient must be considered for bariatric surgery if the OSA is confirmed.[2]

Clinical Summary for Practice

When presenting HbA_{1C} levels are higher, double or triple combinations can be started based on the clinical situation. Symptomatic patients with HbA_{1C}>9% must be started on insulin. When combination therapy fails, a third drug or basal insulin must be added.

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Section 3. Add on Therapy

Question 3

A 65-year-old obese female, known case of T2DM since 4 years, has history of coronary artery disease with hypertension and hyperlipidemia. She has been troubled with 6–7 kg of weight gain over 1 year despite following dietary restrictions and regular exercise. There is history of pancreatitis in the past. Currently she is on 2 g of metformin per day. Her examination reveals the following: BMI 32 kg/m^2; BP 140/80 mmHg; FBS 150 mg/dL; 2 hr PP 220 mg/dL; HbA_{1C} 8.3%; BUN 22 mg/dL; urine albumin–creatinine ratio 180 mg/g of creatinine; serum creatinine 1.2 mg/dL with eGFR 61mL/min; total cholesterol 180 mg/dL; TGL 140 mg/dL; HDL 40 mg/dL. She requests you that she does not want injectables for diabetes control. Which one of the following is the most appropriate next step?

(a) Add pioglitazone 15 mg per day
(b) Add sitagliptin 100 mg/day
(c) Add gliclazide sustained release 30 mg/day
(d) Add canagliflozin 300 mg per day
(e) Add basal insulin 14 units

Discussion

Metformin has a long-standing evidence base for efficacy and safety, is inexpensive, and is regarded by most as the primary first-line treatment for T2DM. When metformin fails to achieve or maintain glycemic goals, various second-line agents are available as an add-on therapy.

All these years, sulfonylureas have been the preferred second agent. With increasing use of incretin therapies as second add-on agent, the cost increases substantially. Long-term benefit of such a shift is not known. Zhang[1] compared outcomes of add on therapy (sulfonylurea, DPP-IV inhibitor, GLP-1 agonist or insulin) for the intensification of metformin monotherapy in 37,000 patients aged at least 40 years with T2DM. Metformin–sulfonylurea combination was the least expensive and resulted in longest time to insulin dependence. However, the study did not account for sulfonylurea-related hypoglycemia. The Glycemia Reduction Approaches in

Diabetes: A Comparative Effectiveness Study (GRADE) is a prospective study comparing same four classes of second-line agents in combination with metformin in 5000 patients with T2DM at 45 US clinical sites for a planned 7-year follow-up. GRADE may provide answers to optimal add on therapy.

Critique of Question 3

Correct Response: d

Metformin monotherapy has failed to achieve optimal glycemic goal. The patient has been struggling to lose weight despite following therapeutic lifestyle changes and being on metformin. Adding gliclazide, pioglitazone, and basal insulin to the regimen may achieve glycemic targets, however at the cost of weight gain. Sitagliptin is weight-neutral; however this patient has had past episode of pancreatitis which asks for a word of caution.

Canagliflozin, SGLT-2 inhibitor, would achieve glycemic target along with weight loss.[2] The efficacy of SGLT2 inhibitors in older (>65 years) T2DM patients has been evaluated in pooled analyses of data from randomized controlled trials. SGLT2 inhibitors have demonstrated reduced HbA_{1C}, body weight, and systolic blood pressure in older patients and were well tolerated, with a safety profile similar to that observed in younger T2DM patients (<65 years).[3] Canagliflozin should not be initiated in patients with an eGFR<60 mL/min/1.73 m^2 (CrCl<60 mL/min). In patients tolerating canagliflozin whose eGFR falls persistently below 60 mL/min/1.73 m^2 (60 mL/min), the dose of canagliflozin should be adjusted to or maintained at 100 mg once daily.[2] While canagliflozin has been shown to increase high-density lipoprotein cholesterol (HDL-C) and decrease triglycerides, body weight, and blood pressure, which potentially decrease CV risk, increases in low-density lipoprotein-cholesterol (LDL-C), which potentially increase CV risk, have been observed. Furthermore, while meta-analysis of randomized clinical trials with canagliflozin did not show an increased incidence of composite CV endpoints, a nonsignificant increase in stroke has been shown.[4–6]

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Section 4. Transitioning to Insulin

Question 4

A 51-year-old woman has T2DM for 4 years. She is currently on glimeperide 3 mg, metformin 1.5 g (SR), vildagliptin 50 mg twice daily. She is also on an ACE inhibitor, statin, calcium, and vitamin D. BP is 130/80 and physical examination is otherwise normal. Her laboratory values are FBS 170 mg/dL, 2 hr PP 240 mg/dL; HbA_{1C} 8.2%; total cholesterol 160 mg%; TGL 150 mg%; HDL 45 mg%. In addition to the re-enforcement of lifestyle changes and education, which one of the following is most appropriate?

(a) Add acarbose 25 mg thrice daily in a titrated fashion.

(b) Add glargine 16 units at bedtime

(c) Substitute liraglutide for vildagliptin

(d) Increase glimeperide to 4 mg

(e) Stop all OHAs and start premixed insulin 30/70

Discussion

Over time, the inexorable march of β-cell dysfunction will catch up with many patients and an OHA will stop being effective. A decision to initiate insulin will have to be made with the patient. Although the use of insulin is beyond the scope of this chapter, the transition to insulin, while bringing in the ability to bring down HbA_{1C} to the desirable levels, also brings in issues like weight gain, inconvenience, and hypoglycemia. Most experts recommend that the best way for patients to bridge to insulin is to start with a small basal dose of either intermediate-acting insulin, like NPH, or a basal analog (glargine, detemir, degludec). This can be given in a convenient bedtime dose that will reduce nocturnal glucose output sufficiently to bring fasting glucose to a level that will allow OHAs to keep daytime glucose within target. If more than two OHAs are on board at the time of transition, it is probably convenient (cheaper) to decrease at least one of the OHAs. Metformin is usually retained because of its long safely, mild weight loss, and possibly protective effect on malignancies. The combination of sulfonylureas and basal insulin forms the basis of the bedtime insulin daytime sulfonylurea therapy (BIDS). Although there is no evidence that this regimen is superior to any other regimen, it has caught

the fancy of many physicians who practice diabetes as a convenient transition protocol. There are early studies attesting to the safety of the combination of DPP-IV inhibitors and GLP-1 agonists with insulin (especially glargine).[1,2]

Glitazones decrease the amount of insulin required but increase weight gain. Safety, as reiterated at several areas, is a particular concern. Many patients will require more intensive regimens.

Critique of Question 4

Correct Response: b

The predominant defect in this patient is fasting hyperglycemia. Acarbose is inappropriate in this situation. Also, it does not have the capability to reduce HbA_{1C} to target. A GLP-1 agonist does not have a significantly greater HbA_{1C} reduction than DPP-IV inhibitors although they confer weight loss. Increasing glimeperide to 4 mg, while reducing FPG somewhat, will be insufficient. While switching to premix is an option, transitioning to insulin can be achieved more acceptably by a single dose of basal insulin.

Clinical Summary for Practice

When OHAs fail, transitioning to insulin becomes necessary. Adding a dose of basal insulin to the existing regimen (NPH or a basal analog) often bridges OHA and intensive insulin therapy.

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CHAPTER 8

Pharmacotherapy with Insulin

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Section 1. Initiating Insulin

Question 1

A 45-year-old man has type 2 diabetes for 5 years. He is on glimepiride 4 mg per day, metformin 1000 mg twice a day, and sitagliptin 100 mg per day. His BMI is 32 kg/m^2. His fasting plasma glucose is 170 mg/dL and the postprandial plasma glucose is 192 mg/dL. The HbA_{1C} is 11%. All other parameters, including lipid profile, cardiac status, renal function, and eye examination are normal.

What is the most appropriate next step?

(a) Add pioglitazone
(b) Add exenatide
(c) Add basal insulin
(d) Add prandial insulin

Discussion

Type 2 diabetes is a heterogeneous disease and is due to defects in both insulin secretion and sensitivity. The United Kingdom Prospective Diabetes Study (UKPDS) has clearly proved the benefits of tight glucose control in preventing onset and progression of microvascular complications of type 2 diabetes; and follow up after the study suggests a favorable trend toward prevention of macrovascular diseases

also.[1,2] This means that aggressive glucose lowering with diet, exercise, and oral hypoglycemic agents (either singly or used in combination) need to be started, and when necessary, insulin needs to be added early on to achieve the goal of glucose control.

When one or two oral drugs are not enough to keep the HbA_{1C} below its target, then usually insulin is prescribed. The common indications for starting insulin in type 2 diabetes are listed in information Box 1.

Choosing between the insulin regimens

Insulin secretion both in the fasting and postmeal state is disordered in diabetes, while it is tightly regulated in normal persons. In the body, insulin is produced in two patterns. One is the constant, *basal* insulin production that occurs throughout the day. This takes care of ongoing metabolic needs. The other is a short spurt of insulin that is produced in response to meals, that is, the bolus pattern. In reality this spurt takes place as two spurts: a rapid-onset first phase (10 minutes) that suppresses hepatic glucose production and a delayed-onset second phase (120 minutes) that actually covers mealtime carbohydrates. All insulin therapy protocols aim to mimic these endogenous patterns.[3] There are several insulin therapy protocols: basal, bolus, basal–bolus, and the premixed regimen. Among these, the pure bolus regimen, also called prandial insulin protocol, is the least useful. This consists of giving short-acting insulin three times a day. The crudest form of this therapy is often seen in the form of the so-called "sliding scales" that are continued to be used in-hospital control. Recently, the 4T study has shown that a bolus-alone regimen can result in more weight gain and hypoglycemia. Thus, as far as practical options go, the choice would rest between the other three regimens: basal, basal–bolus, and the premixed regimen.

Box 1. Insulin therapy in type 2 diabetes: Indications

- When oral antidiabetic agents fail
- Osmotic symptoms and weight loss
- Coexisting moderate/severe infections
- Critical illness
- Pregnancy
- Associated illnesses like cirrhosis
- Surgery
- Renal insufficiency

The *basal regimen* consists of adding one or two doses of long-acting insulin per day. NPH (Neutral Protamine Hagedorn) insulin, detemir or glargine or degludec may be used for this purpose. Oral drugs are continued. The regimen is useful to control fasting glucose levels because the basal insulin suppresses hepatic gluconeogenesis; oral drugs are often needed to prevent postprandial hyperglycemia.

The *basal–bolus* regimen (not the premixed protocol) consists of giving a basal insulin (NPH, glargine, detemir or degludec) in addition to three or more injections of mealtime short-acting insulins (regular insulin, aspart or lispro). This insulin closely mimics endogenous insulin patterns. However, this required more frequent self-monitoring of blood glucose (SMBG). In addition, the number of injections is not well accepted by patients.

The *premixed regimen* uses a combination of regular and NPH insulin in various proportions. The commonest proportion is the 30:70 mixtures of short- and intermediate-acting (NPH) insulin. Analog mixtures using aspart and lispro are also available. For instance biphasic aspart contains 30% aspart and 70% protaminated aspart. Premixed insulin regimens are simple to use, and improve compliance. This is the most commonly used insulin regimen all over the world.

The initiating dose, type, and regimen of insulin depends on various factors:

1. **Is diabetes of very long duration?** In this case, usually the β-cell failure is likely to have advanced significantly, and insulin may need to be given in an intensive manner, that is twice or thrice or four times a day. On the other hand, if diabetes is of relatively short duration, then a basal insulin may suffice.
2. **Is the hyperglycemia in the fasting state?** Wherever the fasting plasma glucose is high, basal insulin may suffice. However, when only the postmeal glucose levels are high, a prandial insulin or even a GLP-1 receptor agonist may be needed. And where fasting and postmeal glucose levels are very high, a premixed, or a basal–bolus insulin may be needed.
3. **What insulin does the patient profile suggest?** For example, simple and convenient ways of starting insulin are with a basal insulin or a premixed insulin. However, if the patient is highly motivated, willing to do several self-monitoring blood checks, and requires flexibility in meal timing, then a basal–bolus regimen may be initiated.

Early insulin initiation

Recent studies have reported that early use of insulin therapy can augment insulin secretion, improve c-peptide response, and thus give "rest" to the β-cell. With these regimens, subjects are able to stop insulin after an early short-term regimen. Indeed, many subjects then maintain normoglycemia on diet and exercise alone. It has been hypothesized that these benefits of early insulin accrue because of the amelioration of "glucose toxicity," a term that describes the toxic effect of hyperglycemia on insulin secretion and action. Amelioration of glucose toxicity and the reduction in the workload on the β-cell due to exogenous insulin could then potentially improve glucose control. While the concept is a promising new strategy that awaits confirmation by larger studies, for the present, initiation of glucose control with insulin cannot be endorsed as the standard of care.

Critique of Question 1

Correct Response: c

In this case the correct answer is option c, that is, adding basal insulin to the existing regimen. Oral agents like glimepiride and pioglitazone would not help in bringing down the A_{1C} from its already high levels. While exenatide does bring down body weight (in this case, the man's BMI is high) and prandial glucose levels, it would not have a remarkable effect on the fasting hyperglycemia of this patient. While premixed insulin is also a reasonable choice, the predominantly fasting hyperglycemia (as compared to the fasting glucose, the postprandial glucose is only slightly higher) makes basal insulin a better choice. Therefore in this gentleman, oral antidiabetic drugs may be continued, and a basal insulin may be added.

Section 2. Intensifying Insulin Therapy

Question 2

A 68-year-old spinster with diabetes for 30 years has been taking NPH insulin injections for the past 5 years. She stays alone, and takes the insulin herself. She has had CABG 6 years ago, and has since been on aspirin, rosuvastatin, and telmisartan, with excellent control of blood pressure. She has had one episode of acute pancreatitis 5 years ago, but CT scan abdomen showed no features of chronic pancreatitis. Clinical examination is unremarkable, and the BMI is 26 kg/m^2. She reports occasional nocturnal hypoglycemia, and her HbA_{1C} is 9.3% with a fasting glucose of 180 mg/dL and a postmeal glucose of 302 mg/dL. She is also on metformin 1 g twice a day and glimepiride 3 mg per day.

What is the most appropriate next step?

(a) Add pioglitazone

(b) Add exenatide

(c) Intensify insulin

(d) Increase dose of glimepiride

Discussion

Whenever a single injection of insulin is not sufficient for glucose control, then two or more injections have to be added. This change in insulin regimen is called “intensification” of insulin therapy. Intensification is different from “optimization” of insulin – this term refers to increasing or decreasing the dose by a few units to achieve control, leaving the essential regimen (once a day or twice a day) unchanged. Intensification is also different from switching – a term that refers to a mere change in the type of insulin, for example, replacing NPH insulin with glargine or replacing glargine with degludec.

In patients with recurrent hypoglycemia, changing from traditional insulin to an analog-based regimen may be helpful. Insulin analogs are designer insulins, which are synthetically manufactured; a few amino acids are altered, or other changes made to improve the pharmacokinetic profiles. Insulin has an A chain and a B chain, and minor changes made in the sequence/structure could have major effects

on insulin action. These insulin analogs are designed to mimic the endogenous insulin profiles in the body. They result in insulin patterns that are more similar to insulin production in the normal human body when compared with exogenous human insulin. However, the high cost and the modest clinical outcome benefits associated with insulin analog therapy mean that these designer insulins need to be used judiciously.[4] There are short-acting analogs like insulin lispro and insulin aspart and glulisine. These are ultra-short acting insulins, which start acting within a few minutes of the injection and last only for about 3–4 hours. They are excellent postprandial glucose regulators. Biphasic lispro and aspart (which contain mixtures of the short-acting analog and an intermediate form of the same analog) are also useful substitutes for twice daily premixed conventional insulin regimens where the postprandial blood glucose control remains problematic.

The long-acting analogs include degludec, glargine, and detemir. Unlike conventional insulins, which rise, peak, and fall after an injection, degludec, glargine, and detemir have a constant, steady level after injection, and are therefore called peakless insulins. This ensures better control, because the peaks of conventional insulins are linked to hypoglycemia; the troughs of the conventional insulins cause hyperglycemic excursions. Degludec is a new basal insulin that can be given once

Box 2. Insulin analogs – A comparison

Analog	Description	Onset (hours)	Peak (hours)	Duration (hours)
Lispro	B28 and B29 amino acids are interchanged to lysine and proline	<0.5	1	3–4
Aspart	Substitution of aspartic acid for proline at position B28	<0.5	1	3–4
Glulisine	Glutamine substituted at B chain beginning, lysine substituted at B chain end	<0.5	1	3–4
Glargine	Two arginines added to B chain and glycine instead of asparagine at A21	2.5	None	24
Detemir	Threonine deleted at B30 and acylation of a C14 fatty acid to lysine at B29	2.5	None	12–24
Degludec	Removal of threonine at B30. At B29, a glutamic acid spacer is attached that bridges to a 16-carbon diacid	<2.5 hr	None	Up to 42 hr

a day in a flexible manner, and though given once a day the effects last for up to 42 hours. This means that degludec can be injected virtually any time of the day, and even if an occasional dose is missed glycemic control may not be affected.[5]

Regardless of the regimen used, "switching" to insulin analogs has been shown to reduce hypoglycemia, and therefore, increasing the chances to reach HbA_{1C} target with minimal hypoglycemia.

Critique of Question 2

Correct Response: c

The correct answer is c. In this elderly lady with a high HbA_{1C} on basal insulin and oral drugs, an intensification, that is, a change in the insulin regimen, is ideal. The new insulin regimen could either be a premix regimen or, ideally, a basal–bolus regimen.[6]

This elderly lady, with a history of pancreatitis, may not be suitable for incretin therapy, given the signal of risk linking incretins with pancreatitis. Pioglitazone can increase risk of fractures, and a postmenopausal state is already putting this patient at a risk of fracture.

In diabetic persons, unable to monitor glucose levels regularly, and seeking convenience over flexibility, premix insulins are a reasonable choice. However, in people with diabetes who are willing to monitor premeal glucose levels and make necessary changes to their targets, basal–bolus insulins are ideal as they offer flexibility.

Finally, given the age, the prior cardiac history, and the occurrence of repeated hypoglycemia, two points may be considered. First, the target for HbA_{1C} control may be relaxed to about 7.5%. Second, an insulin analog based regimen, either basal–bolus analog therapy or a premix analog regimen, may be considered in this case.

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CHAPTER 9

Prevention of Diabetic Nephropathy

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Section 1. Early Detection

Question 1

A 43-year-old man has diabetes for 2 years. He has no significant medical complaints and is asymptomatic. He is currently on metformin SR 1 g at bedtime. Physical examination reveals blood pressure 150/95 mmHg; BMI is 24.66; rest of the examination is unremarkable. Fasting plasma glucose is 112 mg/dL, 2-hour postprandial is 182 mg/dL and HbA_{1C} is 7.1%. Serum creatinine is 1 mg/dL; lipid profile reveals total cholesterol 240 mg/dL, triglycerides (TGL) 200 mg/dL, HDL cholesterol 38 mg/dL, LDL cholesterol 120 mg/dL and VLDL cholesterol 82 mg/dL; urine microalbumin is 65 mg/L. Which one of the following best predicts future risk of nephropathy in this patient?

(a) Diastolic blood pressure > 75 mmHg

(b) HbA_{1C} > 7%

(c) Urinary albumin/creatinine ratio (ACR)/> 30 mg/g

(d) LDL > 100 mg/dL

(e) TGL > 150 mg/dL

Discussion

Chronic renal insufficiency due to type 2 diabetes mellitus (T2DM) is the leading cause of end-stage renal disease (ESRD) worldwide. Diabetic nephropathy (DN) is a microvascular complication of diabetes mellitus, characterized by persistent proteinuria, decline in glomerular filtration rate (GFR), which increases the risk of morbidity and mortality in diabetics. DN has been classically defined by the presence of proteinuria >0.5 g/24 hours. There are approximately 6.6 million patients with DN in India.

Diabetic nephropathy results from many causes, genetic and acquired. Multiple mechanisms contribute to the development and outcomes of DN; these include interaction between hyperglycemia-induced metabolic and hemodynamic changes and genetic predisposition, which sets the stage for kidney injury. It marches through several distinct phases of development. Functional changes occur in the nephron at the level of renal glomerulus, including glomerular hyperfiltration and hyperperfusion, which are the earliest functional preclinical, before the onset of any measurable clinical changes. Subsequently, followed by thickening of the glomerular basement membrane, glomerular hypertrophy and mesangial expansion take place.

A higher proportion of individuals with type 2 diabetes are found to have persistent albuminuria and overt nephropathy shortly after the diagnosis of their diabetes, because diabetes is actually present for many years before the diagnosis is made. Without specific interventions, 20–40% of T2DM patients with persistent albuminuria progress to overt nephropathy, but by 20 years after onset of overt nephropathy, only approximately 20% will have progressed to ESRD. The rates of fall in GFR are again highly variable from one individual to another. Many patients do not progress to ESRD due to high risk of death from CAD before development of ESRD. With better treatment for CAD and increased life expectancy, the prevalence of patients progressing to ESRD is expected to rise.

The earliest clinical evidence of nephropathy is the appearance of microalbuminuria (incipient nephropathy, Table 1). Traditionally, microalbuminuria is defined as albumin excretion of 20−200 μg/min (30–300 mg/24 hours) in a 24-hour sample, or an albumin-to-creatinine ratio greater than 30 mg/g in a first morning midstream sample. Microalbuminuria can also be defined in terms of the urinary albumin-to-creatinine ratio. A ratio greater than 30 mg/g in the first voided sample in the morning (clean, midstream) is considered abnormal. The concentrations of albumin and creatinine in

the first urine in the morning correlate very well with those in 24-hour samples and a 24-hour collection is usually not necessary. If assays for microalbuminuria are not readily available, screening with reagent tablets or dipsticks for microalbumin may be carried out, since they show acceptable sensitivity (95%) and specificity (93%). Urinary albumin levels can vary widely from sample to sample in the same patient. Factors that can increase urinary albumin excretion include urinary tract infection, congestive heart failure, exercise, fever, poor glycemic control, and vaginal discharge, which must, therefore, be excluded before screening for microalbuminuria. At least two elevated albumin-to-creatinine ratios separated by 3 or 6 months are required to make the diagnosis of microalbuminuria.[1]

Up to 7% of patients with T2DM have microalbuminuria at diagnosis. Screening, therefore, is recommended at diagnosis and annually thereafter. In the UKPDS trial, progression to microalbuminuria from diagnosis occurred at 2% per year, from microalbuminuria to macroalbuminuria at 2.8% per year, and from macroalbuminuria to elevated plasma creatinine (≥175 µmol/L) or renal replacement therapy (RRT) at 2.3% per year. Ten years following diagnosis of diabetes, the prevalence of microalbuminuria was 24.9%, macroalbuminuria was 5.3%, and of elevated plasma creatinine or RRT was 0.8%.

Relative risk (RR) of progression to overt nephropathy is twofold higher in patients with microalbuminuria (OR 2.07, 95% CI 1.57–2.74; *P*<0.0001). Microalbuminuria

Table 1. Definition of microalbuminuria

Category	Spot collection (µg/mg creatinine)	24-hr collection (mg/24 hr)	Timed collection (µg/min)
Normal	<30	<30	<20
Microalbuminuria	30–299	30–299	20–199
Clinical albuminuria	≥300	≥300	≥200

Stage	Description	GFR (mL/min/1.73 m^2)
1	Kidney damage with normal or ↑ GFR plus persistent albuminuria	≥ 90
2	Kidney damage with mild ↓ GFR plus persistent albuminuria	60–89
3	Moderate ↓ GFR	30–59
4	Severe ↓ GFR	15–29
5	Kidney failure	< 15 (or dialysis)

also predicts mortality with patients who die with diabetes being more likely to microalbuminuric (*P*=0.016).[2] Without specific interventions, 20–40% patients with T2DM with microalbuminuria will progress to overt nephropathy. Presence of albuminuria is also a marker of increased cardiovascular morbidity and mortality. Microalbuminuria doubles the risk of having a cardiovascular event; the risk is higher than that conferred by established atherosclerotic risk factors.

An important caveat is that a low GFR (<60 mL/min/1.73 m^2) may be present in up to 30% of patients in the absence of micro- or macroalbuminuria and retinopathy. Therefore, in addition to testing for microalbuminuria, patients with diabetes must have an annual estimation of GFR and the patient classified accordingly (Table 2). The recommended method of estimating the GFR is that of the modified diet in renal disease (MDRD): GFR (mL/min/1.73 m^2) = 186 × [serum creatinine (mg/dL)−1.154 × age (years)−0.203 × (0.742 if female)]. A user-friendly way to use this formula is available online (www.kidney.org/klsprofessionals/gfr_calculator.cfm). The Cockroft–Gault equation that is commonly used for estimating creatinine clearance [{140 − age (years)} × weight (kg)/{72 × serum creatinine (mg/dL) × (0.85 if female)}] is less accurate.[3]

Presence of albuminuria is a marker of greatly increased cardiovascular morbidity and mortality, among patients with either T1DM or T2DM. Thus, the finding of microalbuminuria is an indication for screening for possible vascular disease and aggressive intervention to reduce all cardiovascular risk factors (e.g., lowering of LDL-C, antihypertensive therapy, cessation of smoking, institution of exercise, etc.).

Critique of Question 1

Correct Response: c

Hypertension is an independent predictor of nephropathy. In some studies, TGL has also been shown to be a predictor. However, the strongest predictor of future nephropathy is microalbuminuria. The ACR is an excellent approximation of 24-hour urinary microalbumin levels.

Clinical Summary for Practice

Diabetes is the most common cause of ESRD. Microalbuminuria is the strongest predictor of overt nephropathy. Screening for microalbuminuria is recommended at diagnosis and annually thereafter.

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Section 2. Prevention of Diabetic Nephropathy

Question 2

A 56-year-old man has diabetes for 2 years. He is currently on metformin 1.5 g/day. At his annual clinical examination recently, his blood pressure was 140/80 mmHg, BMI 28 with no other abnormalities. Laboratory tests revealed the following: fasting plasma glucose 130 mg/dL, 2 hr postprandial 190 mg/dL and HbA_{1C} 7%; total cholesterol 200 mg/dL, triglycerides 210 mg/dL, HDL-C 35 mg/dL and LDL-C 123 mg/dL; serum creatinine 0.9 mg/dL; urine microalbumin 38 mg/g. Which one of the following strategies will be the most effective in reducing the risk of progression to overt retinopathy?

(a) Adding aspirin 150 mg/day
(b) Adding fenofibrate 200 mg/day
(c) Changing metformin to insulin
(d) Adding ramipril 10 mg/day
(e) Multifactorial intervention

Discussion

Glycemic Control

Tight glycemic control reduces the risk of the development of microalbuminuria and overt nephropathy in people with diabetes. In the UKPDS, intensive blood glucose control resulted in both a 33% reduction in relative risk of development of microalbuminuria or clinical grade proteinuria at 12 years, and a significant reduction in the proportion doubling their plasma creatinine (0.91% vs. 3.52%, $P = 0.0028$).[1] When tight glycemic control is started early, the benefits last longer than actual duration of tight control.[2] On the contrary, when patients who are diabetic for several years are started on intensive therapy, the magnitude of benefit appears to be insignificant.[3]

Several international guidelines have been updated to include incretin-based therapies as treatment options. DPP-4 inhibitors are suitable for use in patients with mild CKD without dose adjustment. Sitagliptin and vildagliptin can be used for mild CKD and, with dose adjustment, in moderate to severe CKD. Saxagliptin can

be used in patients with mild to moderate, but not severe, CKD. Linagliptin can be used safely in CKD patients without dose adjustment. However all gliptins appear to be safe and well tolerated, with a low incidence of adverse effects.

Hypertension

Hypertension is present at the time of diagnosis of diabetes in about one-third of patients. Acceptable targets of therapy appear to be a blood pressure of 130/70 mmHg. Initial treatment should consist of lifestyle modifications including weight loss, reduction of salt and alcohol intake, and exercise. Although reduction in blood pressure with any agent seems to confer benefit, angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers are the therapeutic agents of choice, especially in the presence of microalbuminuria. Cough may be a limiting factor in some patients with ACEIs; angiotensin receptor blockers (ARBs) are suitable alternatives. Thiazide diuretics are useful add-on agents and these may reduce the risk of hyperkalemia seen with ACEIs. Other drugs may be used as required to bring the blood pressure to target.

Renin–Angiotensin System Blockade

Angiotensin-converting enzyme inhibitors reduce the progression from microalbuminuria to macroalbuminuria by about 55%; they also increase the rate of regression from microalbuminuria to normoalbuminuria by about 3.4-fold. In addition, they significantly reduce the risk of all-cause mortality (mainly cardiovascular) by about 20%. This appears to be independent of baseline hypertension, type of diabetes, stage of DN, and duration of treatment.[4] Angiotensin receptor blockers, on the other hand, cause a 22% reduction in the risk of ESRD and doubling of serum creatinine concentration, a 51% reduction in progression rates from microalbuminuria to macroalbuminuria, and about a 42% increase in regression from microalbuminuria to normoalbuminuria.[4] The effect of ACEIs and ARBs appears to be a class effect; choice of agent is dictated by cost and physician preference. There appears to be no additional benefit to combining ACEIs and ARBs.

Others

Replacing red meat with chicken in the usual diet reduced UAE by 46% in microalbuminuric patients with T2DM.[5] A normal protein diet with chicken as the only source of meat may represent an additive strategy for the treatment of microalbuminuric T2DM patients. Protein restriction may be warranted in patients

with overt nephropathy. Therapy of dyslipidemia may also reduce proteinuria and prevent decline in GFR. In the Heart Protection Study, 40 mg simvastatin reduced the rate of GFR decline in patients with diabetes, independent of cholesterol levels at baseline, by 25%.[6]

Multifactorial Intervention

The best approach to preventing DN and its progression is to put all the above-mentioned measures together into practice. In the Steno-2 study, multifactorial intervention was compared with conventional treatment in 160 microalbuminuric T2DM patients. The targets were to achieve blood pressure levels less than 130/80 mmHg, fasting serum cholesterol less than 175 mg/dL, fasting serum triglycerides less than 150 mg/dL, and HbA_{1C} less than 6.5%. The multifactorial intervention consisted of a stepwise implementation of lifestyle changes and pharmacological therapy, including a low-fat diet, a three to five times a week light-to-moderate exercise program, a smoking cessation program, and prescription of ACEIs or ARBs, and aspirin. The intensively treated group had a 61% reduction in the risk of developing macroalbuminuria. There was a 56% reduction in new and worsening nephropathy and an absolute 6% decrease in the need for dialysis (RR 0.39, CI 0.17−87, P<0.003).[7]

Critique of Question 2

Correct Response: e

Aspirin does not worsen DN. Evidence to support a primary role in DN is scant. The reduction of LDL with statins and to some extent reduction of TGL with fibrates also reduce progression to overt nephropathy. Insulin does not appear to confer additional benefit beyond that conferred by good glycemic control. ACEIs are clearly the drugs of choice in the prevention of DN. However, multifactorial intervention, as exemplified by the Steno-2 trial and which includes glycemic control, ACEIs, statins and aspirin, is the best strategy.

Clinical Summary for Practice

Early aggressive glycemic control reduces the risk of progression of nephropathy. Blood pressure control, especially with ACEIs or ARBs, is important. Other measures include control of dyslipidemia. The best strategy is a multifactorial approach as employed in the Steno-2 trial.

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Practice Box

1. Measure albumin/creatinine ratio at diagnosis and annually.
2. Calculate GFR at least annually by this formula: GFR (mL/min/1.73 m^2) = 186 × [serum creatinine (mg/dL)−1.154 × age (years)−0.203 × (0.742 if female)].
3. Calculator is available online at this site: www.kidney.org/klsprofessionals/gfr_calculator.cfm.
4. All patients with microalbuminuria and/or hypertension will benefit from ACE Is or ACE receptor blockers. Combination of the two is not recommended.
5. A multifactorial approach that combines blood pressure, glycemic control, and the use of statins is the best strategy to reduce the risk of nephropathy.

CHAPTER 10

Diabetic Retinopathy

GR Sridhar

Section 1. Screening for Retinopathy

Question 1

A 35-year-old man was diagnosed to have diabetes 4 months ago. He has a BMI of 24.7, is physically active, does not smoke, and is on a dose of 1 g metformin day. HbA_{1C} is 6.8%; total cholesterol is 158 mg/dL; low-density lipoprotein cholesterol (LDL-C) is 100 mg/dL; urine microalbumin is 42 mg/dL. In his clinical evaluation and prognosis, specifically when screening for diabetic retinopathy, which one of the following is correct?

(a) Screening can commence after 10 years since baseline risk for retinopathy is low.

(b) Initial and annual screening by an ophthalmologist is necessary.

(c) Eye examinations are necessary as soon as the patient develops floaters or decreased visual acuity.

(d) A nondilated fundus examination by the primary care physician is a sufficient screening tool.

(e) Seven-field digital photography is the preferred screening tool in all patients.

Discussion

Diabetic retinopathy (DR) is common complication, with more than 60% of subjects eventually having some degree of retinopathy. The major risk factors are duration of diabetes, severity of hyperglycemia, hypertension, and elevated serum lipid levels.[1]

Most patients with DR are asymptomatic until very late stages of the disease. Symptoms, when present, may include decreased visual acuity and contrast sensitivity, new-onset floaters, or dark curtain. Loss of vision may also result from retinal detachment, macular edema, and glaucoma. Other ophthalmologic complications of diabetes include cataract and open-angle glaucoma.

Usually, DR follows an orderly pattern: chronic hyperglycemia results in focal areas of microaneurysms, intraretinal hemorrhages, and focal areas of ischemia (cotton wool spots). It is caused by vascular endothelial dysfunction resulting in a loss of endothelial cells and pericytes. This stage of DR is classified as nonproliferative DR (NPDR). As it progresses, retinopathy becomes widespread with the occurrence of venous beading, intraretinal microvascular abnormalities, and more hemorrhage. This more advanced stage of DR is the severe NDPR, even though visual loss or visual symptoms are uncommon even at this stage. If there is further ischemic injury, fragile new blood vessels grow at the inner retinal surface. When these bleed, floaters may appear which are caused by vitreous hemorrhage. Fibrosis of the vessels may pull back the retina, leading to retinal detachment and visual loss.

Given the asymptomatic nature of DR and the effectiveness of early treatment, subjects should be referred for regular screening by an ophthalmologist. The American Academy of Ophthalmology recommends that patients with type 2 diabetes mellitus (T2DM) be examined at the time of diagnosis and yearly thereafter, and those with type 1 diabetes mellitus (T1DM) be examined 3–5 years after diagnosis and yearly thereafter (Table 1 and Box 1).[2]

The gold standard for the detection of retinopathy is a 30-degree seven standard field stereoscopic photography. Even though it is superior to traditional indirect ophthalmoscopy under mydriatic dilatation as performed by ophthalmologists,[1] it is cumbersome and expensive for routine use. Digital retinal imaging, using single-field or three-field photography without mydriasis, has been shown to be comparable and may be useful. It is especially useful where there is a limited access to ophthalmologists.

Nevertheless, comprehensive eye examination by an ophthalmologist is the preferred modality, especially for initial evaluation and in the follow-up of abnormal findings.

Table 1. Recommended eye examination schedule for patients with diabetes mellitus[2]

Type of diabetes	Recommended time of the first eye examination	Recommended follow-up
T1DM	3–5 years after diagnosis	Yearly
T2DM	At the time of diagnosis	Yearly
Prior to pregnancy (T1DM or T2DM)	Prior to conception and early in the first trimester	No retinopathy to mild-to-moderate NPDR: every 3–12 months Severe NPDR or worse: every 1–3 months

Box 1. Recommended annual eye assessment for the patient with diabetes

- Visual acuity; refraction if indicated
- Measurement of intraocular pressure
- Slit lamp examination
  - Anterior segment, particularly for cataract
  - Macular thickening
- Retinal examination with dilated pupil
  - Ophthalmoscopy, or
  - Retinal photography

Critique of Question 1

Correct Response: b

Unlike T1DM, DR can be present at the diagnosis in patients with T2DM. Most patients are asymptomatic until late in the state of the disease. A floater may be the first indication of vitreous hemorrhage, and thus a late stage to identify DR. Screening for retinopathy is recommended at the diagnosis and annually thereafter. The seven-field digital, although the gold standard, is cumbersome and expensive for routine clinical practice. Digital photography technology that captures a single nondilated field can be used in physician offices and results read by the ophthalmologists by telemedicine where ophthalmology access is unavailable. Comprehensive eye examination by an ophthalmologist is the preferred screening modality.

Clinical Summary for Practice

Diabetic retinopathy is a preventable microvascular complication of diabetes mellitus. Most patients are asymptomatic. Initial and annual examination by an ophthalmologist is recommended.

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Section 2. Management of Diabetic Retinopathy

Question 2

A 56-year-old woman has T2DM for 24 years. She is currently taking a mixed insulin regimen, atenolol 50 mg b.i.d., aspirin 75 mg q.d., and atorvastatin 20 mg q.d. Her glycemic control is erratic and her last HbA_{1C} is 8.1%. She complains of floaters in the eye since 6 months. Blood pressure (BP) is 140/80 mmHg. A dilated fundus examination shows neovascularization, cotton wool spots, and a few hemorrhages (Fig. 1). Which one of the following is the most appropriate next step?

(a) Change to a basal bolus regimen of insulin.
(b) Stop aspirin.
(c) Switch statin to a fibrate.
(d) Switch β-blockers to an angiotensin-converting enzyme (ACE) inhibitor.
(e) Refer for panretinal photocoagulation (PRP).

Discussion

Blindness due to DR is largely preventable by a combination of glycemic and BP control, as well as by the early detection and the treatment of DR with photocoagulation/surgical techniques.

Prevention or delaying of retinopathy is chiefly achieved by good glycemic control and lowering of BP.[1] In the Diabetes Control and Complications Trial (DCCT), intensive blood glucose control reduced the progression of retinopathy by 54%, development of severe NPDR or DPR by 47%, need for laser surgery by 56%, and the risk of macular edema by 23%. The United Kingdom Prospective Diabetes Study (UKPDS) confirmed these results in patients with T2DM. Intensive therapy reduced microvascular endpoints by 25% and the need for laser photocoagulation by 27%. Importantly, in the long-term follow-up, despite near equalization of A_{1C}s following study termination progression of DR remained significantly lower in the former intensive group emphasizing the need for early intervention.[2] In patients with pre-existing proliferative retinopathy, there is an initial risk of worsening when tight control is initiated. In the DCCT, worsening was more common in patients with a higher A_{1C} at baseline and a more rapid reduction; this effect is usually reversed

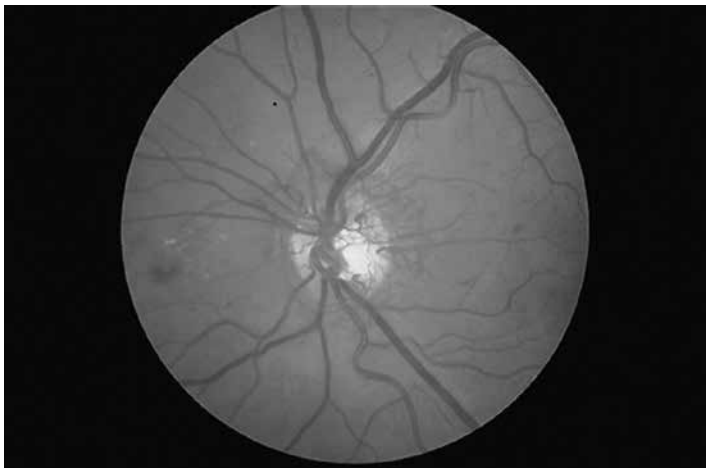

Fig. 1. A dilated fundus examination of the patient showing neovascularization, cotton wool spots, and a few hemorrhages.

within 18 months. No cases of serious visual loss have been reported because of early worsening.

Although no BP is a consistent risk factor for DR incidence and progression, lowering of BP in hypertensive patients leads to slowing of the rate of progression of retinopathy. Irrespective of antihypertensive agent used, lowering of BP to <150/<85 mmHg resulted in a 34% reduction in DR progression and the need for laser treatment and a 47% reduction in the risk of decreased vision.[3] ACE inhibitors may have additional benefit on DR progression independent of BP lowering. Drugs intervening at the level of VEGF have made noninvasive treatment possible for individuals with diabetic retinopathy.[6]

Dyslipidemia may increase the risk of DR. In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, patients treated with fenofibrate were less likely to require laser therapy. In the Collaborative Atorvastatin Diabetes Study (CARDS) study, atorvastatin was not effective in reducing the progression DR. Aspirin appears to have no effect on the DR progression or loss of visual acuity. However, it does not increase the risk of bleeding or vitrectomy. Other agents that purportedly address the pathophysiology of DR including protein kinase C (PKC) inhibitors, aldose reductase inhibitors, growth hormone, etc. have been largely disappointing in clinical trials.

Established secondary interventions for DR include PRP, focal laser photocoagulation, and surgical vitrectomy. PRP, in which laser burns are placed

over the entire retina sparing the central macula, is the cornerstone of treatment for severe NDPR and PDR. The Diabetic Retinopathy Study showed that PRP reduces the risk of vision loss in PDR from 15.9% in untreated eyes to 6.4% in treated eyes. In addition, it showed that there is a regression of neovascularization.[4] The Early Treatment of Diabetic Retinopathy (ETDRS) demonstrated that, when used appropriately and early in severe NPDR and PDR in PRP, the risk of visual loss is reduced to less than 2%.[5] In very severe PDR, early vitrectomy may be beneficial.

Critique of Question 2

Correct Response: e

This patient has proliferative retinopathy. Initiation of tight control may initially worsen the retinopathy. However, no visual loss results from tightening the control and this is desirable in the long run. Aspirin has not been found to worsen retinopathy and may be continued. Fibrates may worsen progress of retinopathy and ACE inhibitors may have additional benefits other than through lowering BP. The treatment of choice, however, is immediate referral to an ophthalmologist for PRP. This will reduce the risk of vision loss which is impending in this patient.

Clinical Summary for Practice

Good glycemic and BP control reduces the progression of retinopathy and decreases the vision loss and need for laser therapy. Patients with severe NDPR and PDR benefit from PRP. An 18-year follow-up of DCCT/EDIC report has shown that at 18 years, the cumulative incidence of retinal outcome is better in the group originally assigned to intensive treatment.[7]

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Practice Box

1. Screen all patients for retinopathy by an ophthalmologist at the diagnosis and then annually.
2. Glycemic control, control of HTN and dyslipidemia are useful in prevention of progression of DR.
3. Proliferative retinopathy requires PRP.

CHAPTER 11

Diabetic Neuropathy

Krishna G. Seshadri

Section 1. Screening Diagnosis and Management of Distal Sensory Neuropathy

Question 1

A 47-year-old person with diabetes for the past 8 years presented with complaints of intermittent burning, stabbing sensation in both his feet for the past 1 year. He has had such sensation on and off for the past 3−4 years but this has been most noticeable and troublesome for the past 1 year. Sometimes, there is numbness and his feet feel "dead" at night. Recently, the burning has been extending up to his knees. He is currently on sitagliptin + metformin 50/1 g b.i.d., glimepiride 2 mg q.d. He is somewhat noncompliant due to frequent travel and his HbA_{1C} has varied from 9.4% to 7.1% in the last 15 months. Currently, his HbA_{1C} is 8.6%. BUN is 22 mg/dL and Cr 0.9 mg/dL. Which one of the following interventions is most likely to provide long-term relief from symptoms?

(a) Tricyclic antidepressants
(b) Serotonin reuptake inhibitors
(c) Stabilization of glycemic control
(d) Anticonvulsant therapy
(e) Aldose reductase inhibitors (ARIs)

Discussion

Diabetic neuropathy (DN) is among the most common complications of diabetes. Its symptoms and manifestations are protean. The major morbidity is foot ulceration leading to gangrene and amputation. Neuropathy, by itself, increases the risk of amputation 1.7-fold; when there is coexistent deformity the risk increases 12-fold.[1] A history of previous ulceration increases the risk of amputation 36-fold. Several classifications exist – the one most used is presented in Box 1. It is important to realize that DN is not a single condition and may be the manifestation of a number of disturbances in the nervous system due to hyperglycemia.

The proximate cause of DN appears to be hyperglycemia. Advanced glycation end-products cause axonal injury. Although animal studies have demonstrated a relationship between increased flux through the polyol pathway and reduced nerve conduction velocity (NCV), human studies with ARIs have been disappointing in terms of demonstrable clinical benefits. Roles for vascular and growth factors, C peptide, and immune mechanism have been suggested.

Focal and multifocal neuropathies are uncommon. Mononeuropathies are usually due to entrapment and can occur at the median, ulnar, peroneal, and lateral femoral cutaneous nerve. Cranial nerves can also be involved, oculomotor being the most frequent. Treatment in these conditions is expectant and supportive. Proximal motor neuropathy (diabetic amyotrophy) presents with pain, wasting, and weakness in the proximal muscles of the lower limbs and usually affects older men. Although

Box 1. Classification of diabetic neuropathy

- Rapidly reversible
  - Hyperglycemic neuropathy
- Persistent symmetrical polyneuropathies
  - Sensorimotor (chronic)
  - Acute sensory
  - Autonomic
- Focal and multifocal neuropathies
  - Cranial
  - Thoracolumbar radiculoneuropathy
  - Focal limb
  - Proximal motor (amyotrophy)
- Superimposed chronic inflammatory demyelinating neuropathy

immunotherapy has been advocated on the basis of pathology, the current therapy remains largely supportive and expectant.

Generalized symmetric polyneuropathies form the bulk of the neuropathies of concern in the diabetic patient.

Rapidly reversible hyperglycemic neuropathy refers to abnormal nerve conduction accompanied by uncomfortable sensory symptoms that occurs in patients with new-onset diabetes or transiently poorly controlled diabetes. They are reversible with restoration of euglycemia.

Acute sensory neuropathy is a variant of symmetric polyneuropathy that is similar to more common, chronic variety discussed below with important differences. It is commonly associated with poor glycemic control, or following hyperglycemic crisis. Conversely, it may occur after improvement in glycemic control (the so-called insulin neuritis – a misnomer). The symptoms are acute or subacute in onset and resolve on achievement of stable control; they last rarely more than a year. Pain is the outstanding complaint in all patients, who also experience severe weight loss, depression, and, frequently in males, erectile dysfunction. Common complaints include constant burning discomfort (especially in the feet), severe hyperesthesia, and deep aching pain. Many experience sudden, sharp, stabbing, or electric shock-like sensations in the lower limbs. All symptoms are prone to nocturnal exacerbation, with bed clothes irritating hyperesthetic skin. Clinical examination is usually relatively normal, with allodynia (pain elicited by stimuli not intended to do so) on sensory testing, a normal motor examination, and occasionally reduced ankle reflexes. Pain control is important and may be achieved as detailed below.

Chronic sensorimotor neuropathy (synonymous with diabetic peripheral neuropathy [DPN]) is the most common variety of DN,[2] usually of insidious onset. It may be present in more than 10% of patients at the time of diagnosis. Up to 50% may be asymptomatic with neurologic deficit detected during a routine neurologic examination or with a complication like a painful foot ulcer. Ten to twenty percent will have symptoms that require therapy.

Symptoms are similar to the acute variety described above but mostly intermittent and less severe. In addition, patients with DPN experience negative symptoms, such as numbness and feet feeling “dead.” Diabetic peripheral neuropathy is a length-dependent process. Its sensory manifestations are most pronounced in the lower limbs and, in more severe cases, in the fingers and hands. Unsteadiness may be present as manifestation of disturbed proprioception and abnormal muscle cell function. Clinical examination reveals symmetric sensory loss to all modalities.

Ankle reflexes may be lost. There is usually no motor deficit and the demonstration of motor deficit must raise suspicion of another pathologic process. A warm dry skin and presence of plantar calluses may indicate the presence of autonomic dysfunction.

The neurologic examination of the lower limbs is the most important aspect of the clinical diagnosis. All patients, irrespective of symptoms, must be screened annually with pinprick, temperature, vibration perception with a 128-Hz tuning fork, the 10-g monofilament pressure sensation, and ankle reflexes. Combinations of more than one test have more than 87% sensitivity in detecting DPN and in predicting future ulcer risk. The feet should be examined for ulcers, calluses, and deformities. Footwear must be inspected.

The Semmes Weinstein monofilament is widely recommended as a tool to detect risk for ulceration. Its use in India is somewhat limited by nonavailability. Testing is done at the hallux and metatarsal head and assesses perception of pressure applied to the handle sufficient to buckle the nylon filament. Sensitivity varies and there is no universal agreement on what constitutes an abnormal test (2/4 or 3/4). Other quantitative tests include vibration perception thresholds, thermal and cooling thresholds, etc., which are rarely required in clinical practice. Nerve conduction velocities are seldom required.

Management

Of all the available treatments, tight and stable glycemic control is probably the only one that will provide symptomatic relief while slowing the progression of neuropathy. While the results are somewhat variable in type 2 diabetes mellitus (T2DM), studies have demonstrated a modest slowing of progression.[3] Since glucose fluxes are the cause of pain, stability rather than actual level of glycemic control may be more important. Tricyclic antidepressants like amitriptyline, serotonin, and noradrenaline reuptake inhibitors (SNRI; duloxetine), newer anticonvulsants like gabapentin and pregabalin, and others like venlafaxine are useful in the control of symptoms in single or in combination. There are no good head-to-head RCTs and therefore the choice of the drug is dictated by physicians' preference. Because of less toxicity and greater tolerability, drugs like gabapentin and pregabalin are widely preferred. None of these measures reverses the progression of disease. The antioxidant alpha lipoic acid administered intravenously is the only pathogenetic therapy that has been validated in clinical trials.[4] Other drugs that target the pathophysiology of DN show improvement in NCV but provide little clinical benefit.

Critique of Question 1

Correct Response: c

This patient has distal sensory symmetric polyneuropathy. At this point of time, the most useful therapy appears to be stabilization of glucose control followed by gradual restoration to normoglycemia. Aldose reductase inhibitors and other therapies, while improving nerve conduction, have not demonstrated clinical improvement. Tricyclic antidepressants and anticonvulsants, while fairly effective in relieving symptoms, do not address the relentless progress of the condition.

Clinical Summary for Practice

Chronic distal sensory neuropathy is the commonest form of DN. It may be asymptomatic and predispose to ulcerations. All patients must be screened for neuropathy at least annually. A good history, use of standardized questionnaires, and clinical examination of pulses, pain, vibration, and touch are able to detect neuropathy effectively in most situations. Stable glycemic control is the most effective therapy. Newer generation anticonvulsants provide effective symptom relief but do not affect progression of neuropathy. Drugs that target the pathophysiology of the disease have been largely disappointing.

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Section 2. Autonomic Neuropathy

Question 2

A 48-year-old woman has diabetes for the past 12 years. She is currently on vildagliptin 50 mg b.i.d. with 1 g of metformin b.i.d. She now presents with light-headedness and weakness. Blood pressure on lying down is 130/85 mmHg, and on standing for 3 minutes, it drops to 90/60 mmHg. There was symmetrical reduction to pinprick in the lower extremity. Pulses were normal. Rest of the physical examination including vestibular testing is normal. Electrolytes are normal. HbA_{1C} is 7.8; TSH is 2. Cortisol level at 8 a.m. is 16 mg/dL. Urine microalbumin is 72 mg. Which one of the following is the most useful in this patient?

(a) Nortriptyline 15 mg at bedtime
(b) Switch oral hypoglycemic agents (OHAs) to insulin
(c) Cinnarizine 8 mg t.i.d.
(d) Midodrine 2.5 mg t.i.d.
(e) Cardiac catheterization

Discussion

Diabetic Autonomic Neuropathy

Diabetic autonomic neuropathy (DAN) is the least recognized and the least understood complication of diabetes. It may exist alone or along with other forms of DN. It involves the entire autonomic nervous system and by default (as the longest nerve of the autonomic nervous system), the vagus nerve, most frequently. The condition is manifested by the dysfunction of one or more organ systems like cardiovascular, gastrointestinal (GI), genitourinary, sudomotor, or ocular. Although subclinical dysfunction can occur, early manifestations are usually several years after the diagnosis of diabetes. Several hypotheses about the pathogenesis exist, none are proven; the process is possibly multifactorial with hyperglycemia contributing to its initiation and worsening. The clinical manifestations are protean and summarized in Box 2.[1]

Box 2. Clinical manifestations of DAN[1]

- Cardiovascular
  - Resting tachycardia
  - Exercise intolerance
  - Orthostatic hypotension
  - Silent MI
- Gastrointestinal
  - Esophageal dysmotility
  - Gastroparesis diabeticorum
  - Constipation
  - Diarrhea
  - Fecal incontinence
- Genitourinary
  - Neurogenic bladder (diabetic cystopathy)
  - Erectile dysfunction
  - Retrograde ejaculation
  - Female sexual dysfunction (e.g., loss of vaginal lubrication)
- Metabolic
  - Hypoglycemia unawareness
  - Hypoglycemia-associated autonomic failure
- Sudomotor
  - Anhidrosis
  - Heat intolerance
  - Gustatory sweating
  - Dry skin
- Pupillary
  - Pupillomotor function impairment (e.g., decreased diameter of dark-adapted pupil)
  - Argyll-Robertson pupil

Cardiovascular manifestations are potentially dangerous. Cardiovascular autonomic neuropathy (CAN) results from damage to the nerves that innervate the heart and its blood vessels. Reduced heart rate variability is the earliest indicator of CAN.[1] In normal individuals, the heart rate increases in inspiration and decreases in expiration. This variability is reduced in DAN. In addition, there is reduced exercise tolerance due to a reduced heart rate, blood pressure, and cardiac output to exercise. Diabetics, suspected to have CAN, must undergo a stress test prior to starting an exercise program.[2]

Orthostatic hypotension (OH) as evidenced by a fall in blood pressure (>20 mmHg systolic and >10 mmHg diastolic) while standing occurs due to damage, especially to efferent sympathetic fibers to the splanchnic vasculature. Patients generally present with light-headedness, dizziness, weakness, fatigue, neck pain, or blurring of vision. This condition must be distinguished from pure autonomic failure (idiopathic OH), hypovolemia, Addison's disease, and hypopituitarism. Therapy is difficult and includes lifestyle changes including avoidance of sudden changes to body position, eating small frequent meals to avoid postprandial hypotension, avoiding activities that increase straining, and avoiding drugs like tricyclic antidepressants that worsen postural hypotension. Midodrine is a peripheral selective α-1 adrenoreceptor agonist approved for the treatment of OH at a dose of 2.5−10 mg t.i.d. Fludrocortisone can be used alternately but is limited by supine hypertension, hypokalemia, and the risk of congestive heart failure. Other therapies include erythropoietin, nonselective β-blockers, and clonidine.

Silent myocardial infarction (MI) is the most feared consequence of CAN. The perception of anginal pain is both diminished and delayed leading to considerable morbidity and mortality. CAN increases cardiovascular mortality (RR = 2.14, CI 1.83–2.51, P<0.0001); [1] the risk increases progressively for each year reaching 23% after 8 years.[3] Several dynamic tests have been designed to detect CAN and have been used for a number of years.[4] These include the following:

- Heart rate response to breathing – the patient lies down and breathes deeply at the rate of six breaths a minute whereas a monitor records the difference between the maximum and minimum heart rates.
- Heart rate response to standing – the patient is connected to an ECG monitor while lying down and while standing to an upright position and tracing are used to determine the ratio between the RR interval during beats 20−40 (longest) and the RR interval during beats 5–25 (shortest).
- Valsalva maneuver – the patient is connected to an ECG monitor and exhales against a fixed resistance with an open glottis; the ratio of the longest RR interval after the procedure to the shortest RR interval during the procedure is calculated.
- Response of diastolic blood pressure to hand grip.

Of these, the deep-breathing test is noninvasive, easy to perform, reliable, reproducible, and has prognostic value.

Glycemic control is useful to reduce progression of CAN in type 1 diabetes mellitus (T1DM). In type 2 diabetes mellitus (T2DM) while the Steno-2 study showed

benefit.[5] This was not evident in the VA cooperative study. Drugs like ACE inhibitors and ARB, while promising, have not been validated in well-designed trials.

Gastrointestinal manifestations include heartburn, dysphagia for solids, early satiety, nausea, vomiting, epigastric discomfort, and bloating. Postprandial hypotension may occur. Drug use including anticholinergics, ganglion blockers, and psychotropic drugs must be excluded. An upper GI endoscopy is warranted to exclude organic causes. If this is excluded, symptomatic therapy with an antiemetic like domperidone or a prokinetic agent such as cisapride is sufficient. Failure to improve with this must prompt specialty referral for further testing like manometry or isotope scintigraphy.

Constipation is the most common GI complication. Diarrhea may occur in up to 20% of patients; it is typically intermittent and may be accompanied by urgency. Bacterial overgrowth due to stasis may contribute. In this situation, a trial of broad-spectrum antibiotics is warranted. Diarrhea may alternate with constipation. Prokinetic agents are preferable to constipating agents. Fecal incontinence, due to sphincter dysfunction, is common in diabetes and may masquerade as diarrhea. Diarrhea may be difficult to treat and may require specialist referral for exclusion of other causes and management.

Genitourinary (GU) symptoms include hesitancy, weak stream, and dribbling and may lead to incomplete bladder emptying progressing on to increased postvoid residual, decreased peak urinary flow rate, overdistension, and finally overflow incontinence. These symptoms are due to the damage of parasympathetic nerves and may predispose patients to UTI.

Erectile dysfunction (ED) is estimated to be present between 35% and 75% of men with diabetes. Besides the limitation in sexual function, ED is also a marker for cardiovascular events. Retrograde ejaculation is also seen. A lack of libido must prompt a work-up for hypogonadism. Glycemic control, smoking, and alcohol cessation are reasonable first steps. A trial of phosphodiesterase inhibitors like sildenafil or tadalafil appears as warranted. These drugs must not be used in patients with ischemic heart disease or on nitrates. In the absence of a response, further work-up to exclude a vascular or neurologic cause is warranted. Women with diabetes may have decreased sexual desire, arousal, and inadequate lubrication.

Another ominous manifestation of DAN is hypoglycemia unawareness. This is discussed in Chapter 19.

Critique of Question 2

Correct Response: d

This patient has OH. OH frequently coexists with neuropathy and may be worsened by drugs used to treat DN. Glycemic control, while desirable, has not been shown to improve DAN in T2DM; specifically paradoxically switching to insulin may worsen OH. Cinnarizine is useful in vestibular disease and has no specific role in OH. Midodrine is the only approved drug that is specifically useful in patients with OH. The presence of CAN predicts cardiovascular mortality. The relationship is, however, less certain with OH; irrespective of this, catheterization is not indicated.

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Practice Box

1. Test for neuropathy in all patients at diagnosis and at least annually.
2. Enquire for symptoms of neuropathy. The following questions may be useful:
   (a) Do you have unsteadiness while walking?
   (b) Do you have burning, aching pain, or tenderness in your legs or feet?
   (c) Do you have prickling sensation in your legs and feet?
   (d) Do you have places of numbness on your legs or feet?
3. Examine:
   (a) Pulses
   (b) Touch
   (c) Temperature
   (d) Pain by pinprick
   (e) Vibration with a 128-Hz tuning fork
4. Educate patient about care of the foot.
5. If therapy is required, newer anticonvulsants, such as gabapentin, are safer (see text).

CHAPTER 12

Cardiovascular Risk Reduction in Diabetes

Pramila Kalra

Section I. Detection and Screening of Cardiovascular Disease in Diabetes

Question 1

A 50-year-old male has type 2 diabetes mellitus (T2DM) for 4 years. He is on glimepride 3 mg once daily and sustained release metformin 1000 mg once daily. He does not smoke or drink. He walks 45 minutes 6 days a week at a brisk pace. He does not have exertional dyspnea or chest discomfort. BP is 130/80 mmHg. HbA_{1C} is 7.0%. Urine albumin is 20 mg/g of creatinine. LDL-C is 95 mg/dL. A resting ECG is normal. He has no family history of premature coronary heart disease (CHD). The patient wants to do some further testing concerning his cardiovascular (CV) system either through blood tests or imaging or both. He wishes to get an opinion regarding the tests needed.

Which one of the following is most appropriate?

(a) No further testing is recommended.

(b) He can be advised a computerized coronary angiogram.

(c) He can be advised a stress thallium test.

(d) A coronary calcium scoring is needed.

(e) One of the newer cardiovascular risk markers should be recommended.

Discussion

Diabetes is a major risk factor worldwide for CHD and has been described as CHD risk equivalent. Cardiovascular disease (CVD) accounts for 50% of mortality in diabetes. Patients with diabetes have accelerated atherosclerosis with increased connective tissue, glycoproteins and calcified plaques. The patients with diabetes have the same CHD risk as non-diabetics with established CHD. About 25% of patients presenting with myocardial infarction (MI) have diabetes. The risk of death is increased twofold in men and four- to fivefold in women.[1] Women who develop diabetes loose most of their inherent protection against the development of CVD.

Mortality rates due to heart disease are two to four times higher among people with diabetes compared with those without diabetes after correction for traditional risk factors for CVD such as age, obesity, smoking, dyslipidemia, and hypertension. Diabetics can get coronary artery disease (CAD) 2 to 3 decades earlier as compared to their nondiabetic counterparts. People with diabetes have up to fivefold higher risk for a first MI and a twofold greater risk for a recurrent MI than people who previously had an MI but do not suffer from diabetes. In addition to CHD, patients with diabetes are also at increased risk for peripheral arterial disease, stroke and arrhythmias.[2] The risk for cardiomyopathy, congestive heart failure, and sudden cardiac death is also increased. The increased risk is present even after adjustment for other cardiac risk factors and individuals with a history of prior coronary events. The global risk scoring systems like Framingham risk score are well-established tools for scoring the risk in nondiabetics but the same is not true for diabetics.

Patients with diabetes have a higher level of coronary artery calcium on imaging and about 55% show stenosis as compared to a population prevalence of 2–4% on angiogram. The American Heart Association Guidelines recommend coronary calcium scoring for asymptomatic diabetics and a myocardial perfusion studies may be recommended for those with a coronary calcium score of more than 400 but the data in this regard is limited.[3] Silent MI is seen in 39% of diabetics as opposed to 22% of nondiabetics. Painless MI is associated with an increased mortality. Painful ST segment depression during exercise testing is twice as common in diabetics. When present, the symptoms of MI or angina are often atypical leading to delay in diagnosis and therapy. Mortality is increased in diabetics presenting with MI or angina when compared with nondiabetics both at 3 months and 1 year. Reasons include greater incidence of anterior infarcts, increased infarct size, higher incidence of CHF and cardiogenic shock (independent of infarct size), and higher rates of reinfarction, myocardial rupture and conduction abnormalities.

The increase in CHD in diabetes is driven by multiple factors; the principal being the increase in "metabolic syndrome" which is directly related to obesity. While patients with diabetes are subject to the same cardiovascular risk factor influences as the general population, there appears to be increased interaction of these risk factors. In addition to traditional risk factors including smoking, dyslipidemia, etc., hyperinsulinemia, changes in platelet aggregation, endothelial dysfunction, and inflammation also appear to contribute.

Cardiovascular risk assessment should begin with a quest for the presence of major risk factors: (1) hypertension, (2) cigarette smoking, (3) dyslipidemia, (4) family history of premature CAD, (5) glycemic control, and (6) renal dysfunction (as evidenced by albuminuria). Other factors need to be taken into account and include excess body weight, increased waist circumference, and lack of physical activity.

A detailed history and physical exam is invaluable. A careful history should include the presence of angina, unexplained dyspnea, and claudication. Physical examination should include blood pressure measurement, assessment of carotid and peripheral arteries for bruits that may indicate peripheral arterial disease and careful cardiac auscultation for added sounds or murmurs. HbA_{1C}, creatinine, urine microalbumin, and fasting lipid profile are sufficient laboratory tests. Tests for Apo B, Apo A and other newer cardiovascular biomarkers are not routinely recommended.

ECG may reveal ischemia, infarction, or left ventricular hypertrophy (LVH). In patients with risk factors resting ECG is a poor predictor of abnormal angiographic results. 2D echocardiograms may reveal regional wall motion abnormalities or LVH. In patients with diabetes who have normal resting ECG, stress testing is abnormal in 16% of patients with 9% having silent coronary disease on angiography.[4] The sensitivity of exercise testing in patients with diabetes is reportedly lower in diabetes. However, asymptomatic patients with negative exercise testing have lower cardiac event rates and more favorable prognosis. In addition routine screening does not appear to affect overall outcome.[5] The coronary computerized tomography may have a potential role in identification of patients with high risk of CAD but no definitive evidence has been shown though few studies have shown good predictive value for risk scoring with this test.[6]

Invasive cardiac testing is recommended in those diabetics with (1) typical or atypical cardiac symptoms or (2) an abnormal resting ECG, (3) for preoperative clearance for major surgery or renal transplantation, and (4) who wish to initiate an exercise program.

The screening of asymptomatic patients with high CVD risk is not recommended as they may already be receiving intensive medical therapy which has been shown to have similar benefits when compared to invasive revascularization. Thus the cost-effectiveness of screening of all diabetics is questionable. The usefulness of recent cardiac screening methods for diabetics beyond risk stratification is controversial.[7,8]

Critique of Question 1

Correct Response: a

The patient is asymptomatic with normal resting ECG and no additional risk factors. While exercise and nuclear testing may reveal latent CAD, there is no evidence to suggest that early detection of CAD in asymptomatic individuals without additional risk factors improves outcomes. Cardiovascular risk reduction through multifactorial approach is recommended for all diabetic patients as outlined below. Screening asymptomatic patients does not appear to be beneficial or cost effective.

Clinical Summary for Practice

Diabetes is a coronary risk equivalent. While a low threshold for testing for CAD is required, routine screening for asymptomatic patients is not recommended.

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Section 2. Risk Reduction Strategies

Question 2

A 52-year-old man has T2DM for 10 years; 6 months prior he had anteroseptal MI following which he underwent coronary revascularization. He does not smoke and quit moderate alcohol consumption after surgery. He walks 45 minutes every day at a brisk pace. He is currently on glimepride 3 mg once daily, metformin 1 g at bedtime and inj glargine 14 units at bedtime. He is also on atorvastatin 20 mg per day, ramipril 5 mg once daily and a combination of clopidogrel and aspirin. He is otherwise asymptomatic; SMBG measurements do not reveal hypoglycemia. His BP is 130/80 mmHg; BMI is 28 kg/m^2. HbA_{1C} is 7.1; LDL-C is 110 mg/dL (initial LDL was 140), TGL is 160 mg/dL, HDL-C is 44 mg/dL; urine albumin is 36 mg/mL. Patient also wants to discuss about bariatric surgery as an option to reduce his CVD risk.

Which one of the following is the most appropriate next step?

(a) Increase glargine to reach an A_{1C} of <6.5%.
(b) Stop aspirin and continue clopidogrel.
(c) Increase statin to reach an LDL-C goal of < 50% of baseline
(d) Add a thiazide diuretic to decrease the BP to <120/75 mmHg.
(e) Add a fibrate to reduce the TGL to <150 mg/dL.
(f) He can be advised for bariatric surgery.

Discussion

The focus of CV risk reduction in T2DM is the detection and management of individual risk factors that contribute to cardiovascular morbidity and mortality in diabetes. There is substantial evidence to show that interventions that target these individual risk factors improve cardiovascular outcomes.

Therapeutic strategies must address physical inactivity, smoking, glycemia, platelet aggregation abnormalities, dyslipidemia, and hypertension.

Physical inactivity is an independent risk factor for CVD and total mortality in patients with diabetes.[1] For each level of inactivity diabetics have a 2.7–3.9 higher CV risk. Regular physical activity has been shown to reduce cardiovascular risk.

The favorable impact is regardless of BMI, blood pressure, cholesterol, and smoking. Various studies have reported 18–45% reduction in CV risk with the highest reduction seen with a total physical activity of 12–21.7 met hours/week. This corresponds to ≈3–5 hours of brisk walking, 2–3 hours of jogging, or 1–2 hours of running.[2] Diabetics should be advised to perform at least 150 min/week of moderate-intensity aerobic physical activity (50–70% of maximum heart rate) spread over at least 3 days of the week with no more than 2 consecutive days without exercise.[3] The low- or moderate-intensity exercises like walking provide all the exercise benefits and a target of 7% of weight loss is recommended.

Patients with diabetes who **smoke** have increased risk of CVD, premature death, and microvascular complications. Smoking may have a role in the development of T2DM. All diabetics who smoke must be counseled and encouraged to quit smoking.[3]

In patients with previous MI, **aspirin** reduces CV morbidity and mortality. Platelet function is undoubtedly altered in diabetes but the protective role of aspirin in the primary prevention of cardiovascular events in diabetes is doubtful. Two randomized controlled trials (RCTs) that specifically addressed primary prevention in diabetes failed to show a beneficial effect.[4] In the general population including diabetics, aspirin reduces the risk of nonfatal MI by 12% but does not appear to reduce risk of cardiac death or stroke.

At this point in time, all patients are benefitted with a projected 10-year CV risk >10% (men>50 or women>60 or anyone with more than one risk factor – family history, hypertension, smoking, dyslipidemia or microalbuminuria).[3] In other patients, the risks of GI bleeding seem to outweigh benefits.

Doses between 75 and 162 mg are recommended. Clopidogrel is indicated in patients who have allergy to aspirin. A combination of aspirin and clopidogrel is indicated in patients for up to 1 year after acute coronary syndrome.

While aspirin resistance appears to be higher in diabetics, this is difficult to document in clinical practice. In women and the elderly there is a higher incidence of nonresponsiveness to aspirin, but there is no recommendation to use other agents in lieu of aspirin.

Glycemic control is crucial to the management of diabetes. Its role, however, in the prevention of cardiovascular risk is controversial. Epidemiologic studies have certainly shown a direct relationship between HbA_{1C} and CVD. Three major trials (ACCORD, VADT, ADVANCE), however, did not show benefit of intensive

therapy in the prevention of cardiovascular events. The glycemic control arm of the ACCORD trial was prematurely terminated because of increased mortality in the intensive control arm. This is in contradiction to the follow-up study of the UKPDS which demonstrated, while at the time of the publication of the original study there was a nonsignificant 16% reduction in MI in the intensive therapy arm, 10 years later, despite near equalization of HbA_{1C} in both arms, the intensive therapy group had significant continued improvements in cardiovascular outcomes (the so-called legacy effect). The reason for the differences in these studies appears to be the duration of diabetes. While mean duration of diabetes in patients enrolled in the ACCORD and VADT trials was greater than 10 years, the UKPDS trial recruited newly diagnosed patients. The implications for practice that emerge from these trials is that aggressive glycemic control targeting HbA_{1C}s to around 6.5 or less is warranted in newly diagnosed diabetics and this may reduce cardiovascular outcomes. A more relaxed target is warranted in patients with comorbidities, established CAD or longer duration of diabetes.

The choice of therapeutic agents in patients with high risk or established CAD deserves mention. While there are no clear guidelines, it is desirable to reduce the risk of hypoglycemia in patients with high risk for CAD. Earlier generation sulfonylureas have been linked in retrospective prescription audits to adverse cardiovascular outcomes. Metformin seems to have proven benefit for CVD risk reduction with no increased risk of heart failure. The cardio protective role of GLP-1 agonists and other incretin mimetics remains to be established in clinical trials. Other aspects of therapy of glycemia and choice of individual agents are detailed in Chapter 7.

The detection and management of **hypertension** in diabetes is detailed in Chapter 7. A goal of 140/90 mmHg is sufficient for most patients with diabetes and hypertension though a lower goal of systolic less than 130 may provide additional beneficial effect on stroke outcome.[3] The recent trials have not shown a benefit of reduction in blood pressure less than 130/80 mmHg as compared to <140/90 on cardiovascular events in patients with T2DM. A J-shaped rather than a linear relationship with CV events has been suggested.[5]

Further lowering as evidenced in the ACCORD trial does not provide additional benefits. ACE inhibitors or angiotensin receptor blockers are preferred.

The detection and management of **dyslipidemia** is detailed in Chapter 14. Strongest evidence exists for lowering of LDL-C as a means to reducing cardiovascular risk. In diabetics with overt CVD, a LDL-C goal of >50% of baseline is desirable. Statins

are the cornerstone of therapy and have demonstrated efficacy backed by major intervention trials. Irrespective of basal lipid levels, statins must be started in (a) patients with overt CVD and (b) diabetics without overt CVD but over the age of 40 and having one or more risk factors. In the event that the goals specified are unmet, the LDL-C must be lowered by at least 30–40% from baseline. Raising HDL-C to >50 mg/dL and lowering triglycerides to <150 mg/dL are secondary targets, but there is no concrete evidence that combination therapy improves outcomes. Statins use is associated with increased HbA_{1C} levels among hypertensive patients and hypertensive patients with diabetes. It should be ensured that the patients with diabetes have their hyperglycemia kept under control.

It is important to take a multifactorial approach to reduce cardiovascular risk (Table 1). The UK Prospective Diabetes Study showed independent and additive effects of glucose and blood pressure on the development of microvascular and macrovascular complications. The more treatment targets reached at baseline, the less likely the risk of new-onset CHD. The Steno 2 study and the SURE study attest to the vital importance of addressing many factors simultaneously. The higher the number of targets reached, the better the outcome: patients achieving ≥3 targets fared better than those achieving ≤2. Interestingly what is good for the macrovascular system also seems good for the microvasculature: in the Steno-2 study, the risk reduction for CVD end points was similar to the reduction for progression of nephropathy and retinopathy.[6] There is irrefutable evidence that cardiovascular risk can be attenuated by structured, intensive, aggressive multifactorial approach.

Table 1. Multifactorial Interventions to Reduce Cardiovascular Risk in Diabetes

• Smoking cessation
• Physical activity – at least 150 min/week of moderate-intensity aerobic activity achieving 50–70% of maximum heart rate
• Use of aspirin (in the appropriate clinical setting)
• Glycemic control that is appropriate for patient's clinical situation
• Control of BP to <140/90; use of ACE inhibitors or ARBs
• LDL reduction to target < 50% of baseline in overt CVD or high risk, < 30% of baseline in others); statin use irrespective of baseline in high-risk patients
• Obstructive sleep apnea to be treated
• Potential role of adequate sleep and avoidance of stress in any form

Other factors which may contribute

Albuminuria

Albuminuria reduction in diabetes to the normal (<30 mg/g) or near-normal range may improve renal and cardiovascular prognosis, but this approach has not been formally evaluated in prospective trials.

Obstructive sleep apnea (OSA)

The association of obstructive sleep apnea with obesity had been shown in the Sleep AHEAD study where 86% of the individuals with T2DM and obesity had OSA. This in turn leads to chronic inflammation, macrophage activation and reduction in adiponectin and increase in leptin leading to increased insulin resistance and thus activating the further pathways.

Melatonin and CVD

Melatonin is secreted after 3–5 hours of sleep and has an anti-inflammatory property; it has been proved beneficial for mitochondrial dysfunction and ischemia reperfusion in cell-based system. Its potential therapeutic implication in the prevention of CVD in diabetics needs to be further studied.[7]

Socioeconomic status

National Health and Nutrition Examination Survey data done from 1998 to 2008 showed an improved cardiovascular risk reduction in diabetics with higher socioeconomic status.[7]

Chronic psychological stress

Any type of stress, for example, psychological, emotional or financial, can lead to increased risk of MI. Allostasis describes a person's capacity to withstand the stress and allostatic load describes the cumulative stress induced physiological dysfunction; a high allostatic load predicts incident of CVD.[7]

Role of Bariatric Surgery

The adipokine modulation after bariatric surgery has been shown to cause reduction in CVD risk factors, CVD and mortality. The reduction in visceral fat after surgery results in decrease in chronic inflammation and may reduce CVD, which further leads to improvement in endothelial dysfunction and insulin resistance. More work is needed to elucidate this relationship.

Concept of Polypill

The concept of polypill, which includes aspirin, atorvastatin and antihypertensive medication in a single pill, has been shown to prevent and reduce CVD and modify the risk factors associated with CVD. The combination pills are well-tolerated and they reduce the relative risk by approximately 60–70%. The widespread use of polypill in primary prevention needs to be more extensively studied.

The use of polypill in secondary prevention is to a great extent in the prevention of nonadherence, improving access to medication and simplification of the treatment algorithm.[8]

Critique of Question 2

Correct Response: c

The ACCORD trial demonstrated that in patients with overt CVD or comorbidities, intensive control may not be beneficial. Therefore lowering the A_{1C} from the current 7.1 may not provide additional benefit in this patient. Combination of clopidogrel and aspirin is appropriate for 1 year after acute coronary syndrome. In primary prevention aspirin alone is indicated if the 10 year risk of CHD is >10%. BP of 140/90 mmHg in patients with diabetes is adequate. Further lowering to <120 systolic may not confer additional benefits. There is no evidence that lowering TGL through the use of fibrates reduces cardiovascular risk. Statins are the mainstay of therapy of dyslipidemia and have the strongest evidence so far. In a patient with overt CVD, LDL should be reduced by > 50% or less and this should be achieved by the use of a higher dose of statin. Increasing the dose of statin is the correct response. This patient should not be advised bariatric surgery as it has to be advised for a BMI of >35 kg/m^2 in patients with T2DM.

Clinical Summary for Practice

Cardiovascular risk reduction is achieved by an aggressive targeted and multifactorial approach to (a) glycemic control, (b) improving physical activity, (c) smoking cessation, (d) controlling blood pressure to <140/90 mmHg and use of ACE inhibitors/ARBs, and (e) reducing LDL-C to < 30% in all patients and < 50% of baseline in patients with overt CVD or at the highest risk of CVD. The use of bariatric surgery for cardiovascular risk reduction in diabetes needs to be evaluated in further studies and should only be advocated for BMI greater than 35 kg/m^2.

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CHAPTER 13

Hypertension in Diabetes

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Section 1. Targets and Initial Management of Hypertension in Diabetes

Question 1

A 44-year-old man with type 2 diabetes mellitus (T2DM) for 3 years is on daily metformin 1 g and atorvastatin 20 mg. He is not a smoker and does not consume alcohol. Blood pressure (BP) is 120/80 mmHg; fasting blood sugar (FBS) is 120 mg/dL, and 2-hour postprandial is 160 mg/dL. HbA_{1C} is 6.9%; BUN is 18 mg/dL; serum creatinine is 0.8 mg/dL; urine microalbumin is 18 mg/mL; and ECG is normal. Which one of the following is appropriate?

(a) Start tablet ramipril 5 mg daily.
(b) Start irbesartan 300 mg daily.
(c) Start amlodipine 2.5 mg daily.
(d) Start a combination of ramipril and irbesartan.
(e) No antihypertensive therapy is required; advise a healthy lifestyle.

Discussion

The prevalence of hypertension (HTN) in patients with T2DM is up to three times greater than those without diabetes. Conversely, patients with HTN have nearly 2.5 times greater risk of developing diabetes. Central obesity, insulin resistance, and

later onset of renal disease, all contribute to the coexistence of the two conditions. Angiotensin-converting enzyme (ACE) inhibitor group of antihypertensive agents appears to reduce the risk of developing diabetes by acting on angiotensin II. On the contrary, the use of β-blockers for the treatment of HTN is associated with a 28% higher risk of developing diabetes.[1]

HTN markedly increases the risk of cardiovascular disease (CVD) in patients with diabetes. Data from controlled clinical trials indicate that the control of BP significantly reduces CVD, stroke morbidity and mortality, as well as development of end-stage renal disease (ESRD) irrespective of the regimen used. However, there has been a moderation in the scope and extent of BP reduction recommended by various professional agencies recently.[2,3]

In the United Kingdom Prospective Diabetes Study (UKPDS), patients who achieved a BP of 144/82 mmHg had significant reductions in diabetes-related end-points including death, stroke, and diabetic retinopathy. A reduction of 34% in the number of patients, requiring photocoagulation and showing deterioration of the retinopathy by two or more steps, was noted. Also seen was a 44% reduction in the incidence of stroke.[4] Every 10 mmHg decrease in mean systolic BP is associated with relative risk reductions of 12% for any complication of diabetes, 15% for deaths related to diabetes, 11% for myocardial infarction (MI), and 13% for microvascular complications. Of note, the degree of CVD reduction achieved by BP control was greater than that achieved by glycemic control.[5] In a subgroup of the Hypertension Optimal Treatment (HOT) trial, a diastolic BP of <80 mmHg was associated with a lower composite CVD outcome.[6] This evidence has been discounted by the Joint National Committee as insufficient. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial demonstrated that further reductions to <120 mmHg systolic may not be beneficial. The ADVANCE trial (treatment with an ACE inhibitor and a thiazide-type diuretic) showed a reduced death rate but not in the composite macrovascular outcome. The ADVANCE trial had no specified targets. The mean SBP in the intensive group (135 mmHg) was not as low as the mean SBP even in the ACCORD standard-therapy group. Based on current data, it is reasonable to target BP to a goal of less than 140/90 mmHg in most of the patients with diabetes. The ADA has revised its target to meet the JNC 8 recommendations. A few patients may be appropriate for a lower systolic BP of <130 mmHg in order to achieve greater reductions in stroke and albuminuria.[7]

Blood pressure must be measured in all patients with diabetes at every clinic visit. The measurement must be done sitting, feet on the floor, and arm supported at the level of the heart after 5 minutes of rest. Cuff size must be appropriate. Patients

who have a systolic BP of ≥140 mmHg or a diastolic BP of ≥90 mmHg must have BP readings repeated on a separate day. A similar reading (systolic BP ≥140 mmHg or a diastolic BP ≥90 mmHg) confirms the diagnosis of HTN in diabetics.

As with the nondiabetic population, target organ damage must be assessed. A fundus examination is mandatory. BUN, creatinine, electrolytes, lipid profile, and uric acid must be measured. ECG and a screening echocardiogram are useful.

Patients with BP>120/80 mmHg should be offered lifestyle modification (LSM), which may include reducing sodium intake to less than 1500 mg/day, increasing consumption of fruit, vegetables, and low-fat dairy products, moderating alcohol consumption, and increasing physical activity. These recommendations are based on data on nondiabetics mostly from the DASH study. There is some evidence to suggest that rigorous salt restriction may be counterproductive in diabetics. Patients who fail LSM or those with initial BP>140/90 mmHg must be in addition started on pharmacologic therapy. The target BP should be <140/90 mmHg.[7]

Reducing BP *per se* irrespective of the regimen used has been demonstrated to improve cardiovascular (CV) outcomes. However, inhibition of the renin-angiotensin system (RAS) through the use of ACE inhibitors or Angiotensin-receptor blockers (ARB) has emerged as the frontline therapy of HTN in diabetes. The Heart Outcomes Prevention Evaluation (HOPE) trial[8] documented decreased CV end-points despite minor changes in BP and suggested that ACE inhibitors have benefits for diabetic patients that are independent of their antihypertensive effect. The Captopril Protection Project (CAPP) trial compared captopril with a β-blocker or a diuretic and showed a 14% lower CV event rate in the ACE inhibitor group. At least two trials have demonstrated the superiority of ACE inhibitors when compared to the dihydropyridine group of calcium channel blockers (DCCB). In both these trials, DCCB use was associated with higher CV events raising conflicting views about their use as monotherapy in diabetes. ARBs have been demonstrated to retard the progress of albuminuria and the development of nephropathy. In 1715 hypertensive patients with nephropathy given irbesartan, amlodipine, or placebo, the relative risk of ESRD was 23% lower in the irbesartan group than in the placebo or amlodipine groups. ARBs, in addition, appear to reduce the risk of congestive heart failure when compared to calcium channel blockers (CCBs). These differences were not explained by the BP reduction achieved. ACE inhibitors and ARBs, when used in normotensive patients with proteinuria, decrease progression to ESRD and also improve CV events. When initiated in patients with microalbuminuria, ACE inhibitors and ARBs reduce the progression to macroalbuminuria; however, it is uncertain whether they confer CV benefits in this setting.

Critique of Question 1

Correct Response: e

In patients with diabetes, HTN is diagnosed when the BP is greater than 140/90 mmHg. Blood pressure reductions reduce CV risk as well as microvascular complications. Blood pressure control with any agent reduces complications. DCCBs like amlodipine, when compared with ACE inhibitors, are not effective in reducing macrovascular outcomes, especially as monotherapy. They may also worsen albuminuria. In addition, ACE inhibitors and ARBs reduce microvascular and macrovascular complications independent of their antihypertensive effects and are widely regarded as first-line agents in diabetics with HTN. ACE inhibitors and ARBs may be useful in normotensive patients with proteinuria and microalbuminuria. They are also indicated irrespective of BP in patients with a previous MI. There are no data to support their use in normotensive diabetics without CVD or microalbuminuria. Reductions in systolic BP below 120 mmHg have not shown to confer benefit in the ACCORD trial.

Clinical Summary for Practice

HTN is a common accompaniment of diabetes and is independently associated with CVD risk. BP>140/90 mmHg is diagnostic of HTN in diabetes. Reduction in BP to this level improves both microvascular and macrovascular outcomes and is recommended. Reductions to levels below a systolic BP of 120 mmHg may not confer additional benefits. ACE inhibitors and ARBs have microvascular and macrovascular benefits independent of their BP-lowering properties and are widely regarded as therapies of choice in diabetics with HTN.

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Section 2. Strategies for Antihypertensive Therapy in Diabetes

Question 2

A 55-year-old man has diabetes for 3 years, on glimepiride 2 mg q.d., metformin sustained release 1 g at bedtime, atorvastatin 20 mg at bedtime, and ramipril 10 mg at bedtime, presents with a sustained BP reading of 150/95 mmHg. He is not a smoker and does not consume alcohol. There are no other significant abnormalities. HbA_{1C} is 7.1; serum potassium is 5.4; urine microalbumin is 44 mg/mL; Cr is 0.8 mg/dL. Which one of the following is the most appropriate next step?

(a) Add irbesartan 300 mg at bedtime.

(b) Switch to enalapril 10 mg at bedtime.

(c) Switch to amlodipine 5 mg after lunch.

(d) Add hydrochlorothiazide 12.5 mg.

(e) Add atenolol 50 mg after breakfast.

Discussion

Treating HTN to target has been shown to reduce both CV and microvascular complications of diabetes. While the JNC 8 recommends use of any of the thiazide diuretics, calcium channel blockers, or ACE inhibitors or ARBS as initial drugs in diabetics without CKD,[1] most diabetologists prefer to use ACE inhibitors or ARBS as drugs of choice. Drugs that target the RAS are the drugs of choice since they seem to afford the greatest protection. ACE inhibitors have long been in use, and are relatively safe, except for cough, which may limit therapy in 5–35% of patients. ARBs are useful in this setting. ARBS have been shown to reduce CHF in patients with T2DM and nephropathy. They are superior to calcium channel blockers in reducing heart failure.[2] Hyperkalemia is a concern with both agents. The risk of hyperkalemia is increased in diabetes because of the predisposition to hyporeninemic hypoaldosteronism. Worsening renal dysfunction may also exacerbate hyperkalemia. Mild increase in serum creatinine may be seen when RAS agents are initiated; moderate-to-higher increase should raise the suspicion of renal artery stenosis. At this time, there is no evidence to support combination of ACE inhibitors and ARBs. In patients who do not tolerate, or who have contraindications

(like angioedema) to the RAS agents, other agents like non-DCCBs (like diltiazem), diuretics, or cardio-selective β-blockers may be used. α-Blockers are associated with a higher incidence of heart failure when used as monotherapy.[3]

One should bear in mind that few patients reach target BP control with one drug. In the United Kingdom Prospective Diabetes Study (UKPDS), three or more drugs were required to achieve a target of 144/82 mmHg. For patients who fail to reach target on ACE inhibitors or ARBs, thiazide diuretics have been traditionally recommended. There is evidence to show that the combination may be synergistic. At small dose, thiazides (<25 mg) do not worsen glucose control and may offset the hyperkalemia caused by ACE inhibitors/ARBs. It must be noted that thiazides are not useful when the estimated GFR (eGFR) is <30 mL/min/1.73 m^2; a loop diuretic must be used for those with an eGFR<30 mL/min/1.73 m^2. In the ADVANCE trial, a fixed dose combination of perindopril and indapamide significantly reduced combined microvascular and macrovascular outcomes, as well as CVD and total mortality.[4] Periodic monitoring of serum creatinine and potassium is recommended by some authorities.

CCBs (irrespective of class) may be used if thiazides are not indicated or tolerated. They are safe and effective in combination with ACE inhibitors/ARBs. α-Blockers are potent antihypertensives and can be used. It is debatable whether two or more drugs should be started together, or if a drug should be maximized before the addition of another drug or if additions should be made with submaximal doses. Early combinations allow accruing benefits from differing modes of action while reducing adverse events; the flip side is the need for more medications in patients who are already on six to eight drugs. There is no clear guidance on this issue.[1]

Critique of Question 2

Correct Response: d

Most patients require more than one medication to achieve targets. Both ARBs and ACE inhibitors are mild antihypertensive agents and are preferred as first-line because of additional CV and renal benefits. Addition of ARB to ACE inhibitors has not shown to improve renal outcomes. In this patient with potassium at the upper limit of normal, the addition of ARB increases the probability of severe hyperkalemia. Both ramipril and enalapril are comparable in the BP-lowering effects; changing to enalapril offers little value. Although both amlodipine and β-blockers can be added to ACE inhibitors, they are not recommended as monotherapy in this setting. Thiazides are synergistic with ACE inhibitors; in addition to reducing BP they also

offset the risk of hyperkalemia and hence appropriate as add-on therapy in this patient.

Clinical Summary for Practice

Angiotensin-converting enzyme inhibitors or ARBs are ideal first-line agents. Most patients require additional therapy to reach targets. Thiazide diuretics are recommended as add-ons. Other classes of drugs may be added to reach a goal of 140/90 mmHg.

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Practice Box

1. Measure BP at every visit.
2. Measure renal functions and microalbumin.
3. Consider lifestyle changes in all patients. Value of tight salt restriction is questioned.
4. If microalbuminuria is present, start ACE inhibitor or ARBs irrespective of BP.
5. If BP is >140/90, start ACE inhibitor or ARBs.
6. Goal is BP<140/90.
7. If BP is not to target, add 12.5 mg of hydrochlorothiazide. Do not exceed 25 mg/day.
8. Consider adding CCBs (nondihydropyridine), α- or β-blocker if BP is still not to target.
9. If BP is not controlled with three or more drugs, consider evaluation for secondary hypertension or referral to a specialist.

CHAPTER 14

Dyslipidemia in Diabetes

Krishna G. Seshadri

Section 1. Approach to Dyslipidemia in Diabetes

Question 1

A 48-year-old man has type 2 diabetes mellitus (T2DM) for 6 years. He presents to his clinician for an annual physical examination. He is asymptomatic. He smokes one pack of cigarettes a day. He is currently on glimepiride 2 mg 1-0-0, metformin 1 g at bedtime. His BP is 130/80 mmHg on 5 mg of ramipril. There are no abnormalities. FBS is 110; 2h PP is 150; HbA_{1C} is 6.7. Total cholesterol is 240; triglyceride (TGL) is 180; and high-density lipoprotein cholesterol (HDL-C) is 30. Which one of the following is the priority in this patient?

(a) Start high-intensity statin to reduce low-density lipoprotein cholesterol (LDL-C) <50% of initial value.

(b) Start moderate-intensity statin to reduce LDL-C to <30% of initial value.

(c) Start lowest tolerable dose of statin.

(d) Start combination of statin + ezetemibe.

(e) Lifestyle recommendations are sufficient as he has no cardiovascular disease (CVD).

The contribution of Dr. S. Das to this chapter in the previous edition is gratefully acknowledged.

Discussion

Diabetes is associated with a two- to fourfold increase in vascular disease with CVD being the primary cause of death. A significant proportion of this risk is contributed by the increased prevalence of lipid abnormalities.

Type 2 diabetes is associated with a cluster of interrelated plasma lipid and lipoprotein abnormalities including reduced HDL-C, a predominance of small dense LDL particles, and elevated TGL. Low levels of HDL associated with elevated TGL are the most prevalent dyslipidemia in patients with T2DM. These changes are also a feature of the metabolic syndrome. LDL elevations in diabetics are similar to those found in the general population. There is evidence that each of these lipid alterations is associated with an increased risk of cardiovascular disease.

All patients with diabetes must have a lipid profile measured annually.[1] This is done after an overnight fast preferably after 12 hours of no food intake except water. Lipid levels are affected by acute stress like surgery, fever, and myocardial infarction (MI). The laboratory measures the total cholesterol (TC), TGL, and HDL-C. LDL-C is calculated using the Friedewald equation: LDL = TC – HDL – TGL/5 mg/dL. This formula is not useful for TGL>400. A related calculation that is believed to approximate the total atherogenic lipoprotein fraction is the non-HDL-C and is calculated by subtracting the HDL-C from the total cholesterol. The non-HDL-C is considered to be a good approximation of apoB. In the highest risk groups, the AHA also recommends measure of ApoB levels;[2] this is not feasible in most practices in India. In patients who have lipids within desirable levels, biannual evaluation is recommended.

Lifestyle modification focusing on the reduction of saturated fat, trans fat, and cholesterol intake, increase of omega-3 fatty acids, viscous fiber, and plant stanols/sterols, weight loss (if indicated), and increased physical activity should be recommended to improve the lipid profile in patients with diabetes. Clinical trials that have been published in the last two decades have consistently shown that pharmacologic therapy aimed at reducing LDL through the use of statins reduces the risk of coronary artery disease. The benefits are the highest in patients with either known CVD or high LDL levels; the gains seen in patients with modest risk for CVD are also significant. Importantly, this benefit appears to occur irrespective of the initial LDL. For each mmol/L reduction in LDL cholesterol there is a 9% reduction in all cause mortality and a 13% reduction in vascular mortality (1) (table 1)

Table 1. Major clinical trials that demonstrate a benefit of statin therapy in T2DM

Study	Drug/dose	LDL reduction and percent	RRR % (ARR%)
Secondary prevention studies			
4S DM	Simvastatin 20/40	186–119 (36)	50 (42.5)
ASPEN	Atorvastatin 10 mg	112–79 (29)	34 (15)
HPS DM	Simvastatin 40 mg	123–84 (31)	17 (7.5)
CARE DM	Pravastatin 40 mg	136–99 (27)	13 (5.4)
TNT DM	Atorvastatin 80 mg*	99–77 (22)	18 (4.7)
Primary prevention studies			
HPS DM	Simvastatin 40 mg	124–86 (31)	34 (6)
CARDS	Atorvastatin 10 mg	118–71 (40)	35 (4)
ASPEN	Atorvastatin 10 mg	114–80 (30)	19 (1.9)
ASCOT DM	Atorvastatin 10 mg	125–82 (34)	8 (0.9)

Modified from Ref. 3.
**Vs Atorvastatin 10 mg*

The AHA ACC joint statement identifies diabetic individuals between ages 40 and 75 as one of the four groups that will benefit from statin therapy (level of evidence A).[2] In a significant departure from goal-based therapy, the AHA ACC joint statement recommended that patients established CAD or greater than 7.5 % 10-year risk for MI be prescribed a high-intensity statin aimed at reducing the LDL by greater than 50% (level of evidence B). Diabetics between the ages of 40 and 75 would benefit by use of a moderate intensity statin aimed at reducing the LDL by greater than 30– 50%. The use of statins in younger and older patients must be individualized based on CVD risk. High-intensity statin in the elderly is not supported by evidence.

High-intensity statins included atorvastatin in the doses of 40–80 mg (usually the latter) and rosuvastatin 20–40 mg. Moderate intensity statins include atorvastatin 10–20 mg, rosuvastatin 5–10 mg, simvastatin 20–40 mg and pravastatin 40–80 mg.

The ADA has revised its recommendations in 2015 in alignment with these recommendations in 2015. It recommends moderate risk statins for patients. Since patients with diabetes are already at high risk for CVD the risk calculator recommended by the AHA has little use (3)

Factors that influence statin therapy include hepatic or renal disease, statin intolerance in the past or age >75. Baseline or routine periodic creatinine kinase (CPK) is not recommended unless there is a history of muscle disorders or there are symptoms during therapy. Baseline alanine aminotransferase (ALT) measurement is recommended but further levels are not required unless the patient is symptomatic on therapy. Statin dose may be reduced if two consecutive values are <40; however there is no data to suggest that such levels are harmful. Statins are contraindicated in pregnancy.

Patients who are started on statins may be retested in 4–12 weeks to gauge response to therapy. High-intensity statins will reduce the LDL by >50% and the LDL is usually less than 100. Adherence is the most common cause of nonresponse although biologic variability in response is well known. A nonstatin may be added to high-risk patients who have less than added response, or who are intolerant to statins. At this time there is little evidence to suggest that there are benefits to addition of nonstatin therapy.

Very little clinical trial evidence exists for patients with T2DM under the age 40 years or for patients with type 1 diabetes mellitus (T1DM) of any age.

Critique of Question 1

Correct Response: a

While this patient has no CVD, his 10-year risk for MI is 28% (calculation can be done through this link: http://cvdrisk.nhlbi.nih.gov). While still the subject of controversy, the ACC AHA ADA guidelines have sufficient evidence base to adopt them in routine practice. Patients with overt CVD or those with a 10-year risk of CVD events of >28% should be started on therapy that will reduce the LDL level to less than 50% of the initial value. Other patients between 40 and 75 will benefit from moderate intensity statins that reduced LDL to less than 30% of the initial value. Uptitration of statin dose from lowest to highest is used by some practitioners but is not recommended. There is no particular advantage to adding nonstatins to statin therapy. While lifestyle is important, it is not a substitute for statin therapy given the significant reductions in CV outcomes achieved.

Clinical Summary for Practice

Dyslipidemia contributes significantly to cardiovascular risk in diabetes. Lipid profile must be measured in all diabetics annually. LDL is the primary target for therapy. Most diabetic patients between the ages of 40 and 75 are candidates for statin therapy. Patients with the highest risk will benefit by lowering the LDL to <50% of baseline while others will benefit by lowering LDL to <30% of baseline through statin therapy.

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Section 2. Beyond LDL

Question 2

A 56-year-old woman has T2DM for 4 years. She is currently on glimepiride 2 mg, metformin SR 1 g, simvastatin 40 mg, and enalapril 10 mg q.d. At her most recent visit, the following laboratory parameters were available: FBS 162, 2h PP 228, HbA_{1C} 7.6, TC 154, TGL 190, HDL-C 38, and LDL-C 78. Which one of the following is the most appropriate next step?

(a) Add fenofibrate 200 mg q.d.

(b) Add niacin and titrate to a dose of 2 g daily.

(c) Increase glimepiride to 3 mg.

(d) Decrease simvastatin to 20 mg.

(e) Add ezetimibe.

Discussion

The robust data that support LDL lowering is missing for both lowering TGL and increasing HDL. Triglyceride levels <150 mg/dL and HDL-C >40 mg/dL in men and >50 mg/dL in women are desirable. In the absence of severe hypertriglyceridemia, therapy targeting HDL-C or TGL has intuitive appeal but lacks the evidence base of statin therapy. Therefore, unless there is an impending risk of pancreatitis, where TGL lowering is imperative, addressing LDL remains the priority. Tight glycemic control will lower TGL significantly and must be tried prior to pharmaceutical therapy. When required, fibrates are superior to other agents in lowering TGL. Should TGL lowering or HDL raising be attempted after achieving LDL goals? There is insufficient data to support such an action. In the ACCORD trial, the combination of fenofibrate and simvastatin did not reduce the rate of fatal cardiovascular events, nonfatal MI, or nonfatal stroke, as compared with simvastatin alone, in patients with T2DM who were at a high risk for CVD. However, prespecified subgroup analyses suggested heterogeneity in treatment effects according to sex, with a benefit for men and possible harm for women, and a possible benefit of combination therapy for patients with both triglyceride level ≥204 mg/dL and HDL-C level ≤34 mg/dL.[1] Similarly, niacin is the most effective pharmacological agent to increase HDL that is available. The AIM-HIGH trial which was designed to discern a beneficial effect of the addition of niacin to a statin failed to demonstrate any additional benefit to

HDL raising. In addition, there was a slightly increased stroke risk in the niacin group. Although HDL raising is desirable, pharmacologic measures to raise HDL are probably not warranted at this time.

Critique of Question 2

Correct Response: c

In this patient with modest TGL elevation, control of glycemia is the most appropriate intervention to lower TGL. While intuitive, very little data support the additional lowering of TGL in patients with desirable LDL by use of fibrates. Clinical trials also do not support the role of ezetimibe as add-on therapy. Further LDL lowering that will be achieved by ezetimibe is not required in this patient. Although higher HDLs protect against CAD, pharmacologically raising HDL by adding niacin has not shown to be beneficial.

Clinical Summary for Practice

Therapy directed at lowering TGL or raising HDL as a specific CV risk reduction strategy lacks scientific basis. In a subset of patients whose LDL is within desirable levels and TGL is more than 234, an addition of fenofibrate was demonstrated but this evidence is not sufficient to translate into practice.

Reference

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Practice Box

1. Fasting lipid profile is recommended in all patients at diagnosis. Repeat biannually if the levels are desirable.
2. If TGL is >600, use fibrate to lower TGL as the risk of pancreatitis is high.
3. In all other patients, LDL lowering is the priority.
4. Start high intensity statins in all patients with CVD or risk of MI>7.5 in 10 years.
5. Start moderate intensity statins in other patients with diabetes between 40 and 75 years.
6. In patients <40 years, consider statins if LDL is >100.
7. HDL raising and TGL lowering do not have sufficient evidence.

CHAPTER 15

Perioperative Management of Diabetes

KM Prasanna Kumar, Radha T. Reddy

Section 1. Perioperative Management of Diabetes

Question 1

A 65-year-old female with type 2 diabetes mellitus (T2DM) is scheduled for a mastectomy for breast cancer in 2 days after cardiac clearance and diabetic control. She had diabetes for the last 15 years, with associated hypertension, hyperlipidemia, non-proliferative stable retinopathy, stage 3 chronic kidney disease, and mild neuropathy. She is currently on glipizide 5 mg bid, metformin 1 g bid, and pioglitazone 30 mg per day for her diabetes. On this regimen, her blood glucose is between 150 and 220 mg/dL fasting, 200 and 350 mg/dL postprandial, and her recent HbA_{1C} is 10.2%. She has had no recent hypoglycemia. The patient is only somewhat compliant with her diet and exercise and is not overly concerned about her glycemic control. You would advise the patient with which of the following regarding her diabetes management?

(a) Continue current regimen and initiate insulin postoperatively.

(b) Increase glipizide to 10 mg bid, continue other oral agents till morning of surgery.

(c) Continue oral agents and start a glucagon-like peptide-1 (GLP-1) agonist.

(d) Start subcutaneous short-acting sliding scale insulin and continue oral agents till morning of surgery.

(e) Initiate basal, bolus, and correctional insulin and continue oral agents till morning of surgery.

Discussion

An estimated 25% of diabetic patients require surgery. Mortality rates are five times higher in a diabetic compared to a nondiabetic, related to end-organ damage caused by diabetes. Infections account for 66% of postoperative complications and nearly a quarter of preoperative deaths in patients with DM. Intensive glycemic control (blood glucose 80−110 mg/dL) in the perioperative period is associated with reduction in length of hospital stay, wound infection, and complications.[1,2] The data on mortality are variable with intensive glycemic control, and there is a significant increased risk of hypoglycemia (blood glucose <70 mg/dL).[3−5] A more relaxed blood glucose target of 140−180 mg/dL decreases morbidity, does not increase mortality, and reduces hypoglycemia risk.

Metabolic Response to Anesthesia and Surgery

Surgery induces a considerable stress response through the release of catecholamines, glucagon, and cortisol. This compensatory mechanism is impaired in diabetic patients necessitating supplemental insulin in the perioperative period. Thus, patients with type 1 diabetes mellitus (T1DM) usually require intravenous insulin therapy depending on the nature of surgery and are more predisposed to end-organ complications than patients with T2DM. Patients with T2DM will need to have their oral hypoglycemic drugs discontinued preoperatively, with intravenous insulin or subcutaneous insulin administered as dictated by the extent of the procedure.

Even nondiabetic patients, because of the considerable stress response, may become hyperglycemic perioperatively. Multiple randomized controlled studies have shown that controlling serum glucose levels in all patients, not merely those with diabetes mellitus, impacts the outcome of surgical patients who are critically ill.

Anesthetic agents can affect glucose metabolism through the modulation of sympathetic tone; in-vitro data suggest that inhalational agents suppress insulin secretion. The resulting relative insulin deficiency often leads to hyperglycemia, raising the risk of ketoacidosis.

General Perioperative Management

A comprehensive history and physical examination is essential. In high-risk populations, it may be prudent to screen all patients undergoing intermediate or major surgery by checking HbA_{1C}. A preoperative HbA_{1C} of 7% or less is ideal. Preoperative treatment of diabetes depends on the type of diabetes, duration of

diabetes, specific medication regimen, current blood glucose concentration, type, duration and severity of surgery, duration of NPO (nil per os or nothing by mouth) and addressing caloric intake. Blood glucose monitoring should be continued frequently so that appropriate action may be taken.

Given that patients present preoperatively with a variety of diabetes mellitus regimens and are scheduled for surgery at varying times of the day, there is no established consensus for optimal perioperative management. Patients should communicate specifics of their surgical procedure to their endocrinologist or internist and, in conjunction with their anesthesiologist, be advised on modifications to their current regimen. Goals of management should include avoidance of hypoglycemia, severe hyperglycemia, volume depletion, electrolyte disturbances, and ensuring adequate nutrition.

Although most patients will have T2DM, many will require insulin therapy, at least temporarily, during the perioperative period. Noninsulin antihyperglycemic agents are not appropriate in most hospitalized patients who require treatment for hyperglycemia. In such patients, insulin may be given subcutaneously as an intermediate-acting insulin, such as neutral protamine Hagedorn (NPH), or long-acting insulin, such as glargine or detemir, combined with premeal rapid or short-acting insulin in patients who are eating regular meals (i.e., basal-bolus regimen). In those who are NPO for short periods, a back-up correction insulin sliding scale using regular or short-acting analog may be used. For patients who are NPO for prolonged periods of time or critically ill, intravenous insulin infusion is the preferred method for achieving and maintaining glycemic control. The key point is that the patient should have at least a small amount of insulin circulating at all times, which will significantly increase the likelihood of glycemic control during the illness.

Guidelines for Glycemic Control

- In general, on the day of surgery, patients on oral regimens should be advised to discontinue these medications.
- Ideally, scheduled subcutaneous insulin with basal, nutritional, and correction components should be started preoperatively for achieving and maintaining glucose control. This regimen is continued till the patient is stable, eating well or till the time of discharge.
- Subcutaneous sliding scale insulin with regular insulin or a short-acting analog can be used for the same day surgery. Prolonged use of subcutaneous sliding scale insulin, as the sole therapy, is not recommended as there is evidence for lack of benefit and potential harm.

- Once the general condition of the patient is stable and he/she is eating, oral agents may be restarted. Additional subcutaneous sliding scale insulin should be used to provide the correctional component.
- Appropriateness of oral agents must be reassessed because of potential complications:
  - Alpha glucosidase inhibitors – no benefit, if NPO
  - Secretagogues (sulfonylureas, meglitinides) – hypoglycemia, prolonged action
  - Metformin – lactic acidosis, caution in renal, hepatic, and cardiac failure
  - Thiazolidinediones – edema, congestive heart failure
  - Dipeptidyl peptidase-4 inhibitors – dosage reduction for renal failure
- In case of prolonged surgery, prolonged NPO or postoperative critically ill patients, intravenous insulin infusion is the preferred method.
- Validated insulin infusion protocols with demonstrated efficacy and safety, and with low rates of hypoglycemia, are recommended.
- With intravenous insulin therapy, frequent glucose monitoring is essential to minimize the occurrence of hypoglycemia and to achieve optimal glucose control.
- Patients with T1DM should be scheduled as first case in the morning for elective surgeries. Patient may be advised to reduce their bedtime dose of insulin the night before surgery to prevent hypoglycemia, while NPO and administer one half of their daily dose of long-acting insulin in the morning. Patient should arrive early to monitor his/her blood glucose and determine the need for intravenous dextrose.

Goals for Perioperative Glycemic Control

The goals for glycemic control are tailored to each patient based on a number of factors, such as the nature and duration of the surgery, severity of the underlying illness, modality used to achieve glycemic control, patient age, and sensitivity to insulin. Numerous clinical trials have involved various patient populations and examined the implications of perioperative hyperglycemia. An HbA_{1C} of 7% or less is ideal for patients prior to elective surgery. But it is practically very difficult to achieve HBA_{1C} <7% in all patients undergoing elective surgery even with multiple doses of insulin. Thus a pragmatic approach is to have plasma glucose values 100–180 mg/dL. Checking premeal is good enough to certify a patient for elective

surgery if he is on insulin . Hypoglycemia before, during and immediately after surgery is a bigger problem than hyperglycemia.

Critique of Question 1

Correct Response: e

In this patient, the preoperative glycemic control is extremely poor. Data suggest that good glycemia in the perioperative period improves outcomes. This patient is on maximum dose of oral antihyperglycemic agents. Waiting till after surgery to initiate insulin is too late. Subcutaneous sliding scale with short-acting insulin and continuation of her oral agents will not be adequate to control her blood sugars. This is because it is a retrospective correction and will be used only when the blood glucose levels are high. This can result in premeal hypoglycemia with the next meal if insulin is too much. On the other hand, if the blood glucose is normal, patient will not receive any mealtime insulin, resulting in high blood glucose prior to the next meal, resulting in a roller coaster pattern of blood glucose. It can potentially do more harm by giving a false sense of security that patient is on some insulin. Increasing glipizide to maximum effective dose will not be adequate to control the blood glucose. GLP-1 agonists will not be effective given the short duration of time prior to surgery. Hence, the choice e offers the best chance of optimizing her blood glucose prior to surgery and maintaining glycemia postoperatively.

Clinical Summary for Practice

Both hyperglycemia and hypoglycemia are the markers of poor outcome in perioperative patients. The current consensus from the ADA recommends keeping perioperative blood glucose between 90 and 180 mg/dL in most perioperative patients to avoid hypoglycemia and severe hyperglycemia. All noninsulin antihyperglycemic agents should be discontinued on the morning of surgery. Patients with T1DM require insulin all the time. Insulin is the preferred antihyperglycemic agent perioperatively in type 2 diabetics also. It should be administered as subcutaneous bolus-basal regimen or as intravenous infusion therapy. Subcutaneous sliding scale insulin, as monotherapy for prolonged periods, may be ineffective and actually do harm.

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Practice Box

1. Assess complexity of surgery, need for nil per oral and its duration, and current glycemic control.
2. Most OHAs will need to be discontinued prior to surgery.
3. Insulin is the safest agent in the perioperative period. A short-acting insulin may be used either subcutaneously or through an infusion adjusted to maintain a capillary blood glucose between 120 and 180.
4. In the post-operative period, insulin may be used until the patient is able to eat. A basal insulin, to prevent ketosis with regular insulin on demand, is preferred.
5. Transition to OHAs may be done prior to discharge depending on the intake.

CHAPTER 16

Diabetes in the Hospitalized Patient

Krishna G. Seshadri

Section 1. Hospital Management of the Diabetes Patients

Question 1

A 52-year-old woman is admitted to the hospital for acute exacerbation of bronchial asthma. At home, she is taking inhaled β-agonists and inhaled steroids. Her last diabetes check was 1 month prior and her $HbA1_c$ was 7.5. At home, she is taking glimepiride 2 mg in the morning and sustained release metformin 1 g at bedtime. She is admitted and started on intravenous methylprednisolone. Twenty-four hours after admission, she still has wheezes and may require 2–3 days more of high-dose steroids in the hospital. Capillary blood glucoses (CBGs) done every 4 hours on the first day are around 250–300. She was nil per oral for the first 16 hours but has been told that she can start oral intake this morning. Which one of the following is the most appropriate in terms of glucose management for the remainder of the hospital stay?

(a) Restart home oral medications.

(b) Start glimepiride and bedtime insulin but not metformin.

(c) Start basal and premeal insulin with supplemental insulin.

(d) Start sliding scale insulin.

(e) Hold metformin and add thiazolidinedione to home medication.

Discussion

A disproportionate number of hospitalized patients have diabetes. For every two patients in the hospital with known diabetes, there may be an additional patient with newly observed hyperglycemia. Hyperglycemia in the hospital may result from stress, decompensation of diabetes and/or may be iatrogenic due to administration of pharmacologic agents including glucocorticoids, vasopressors, etc. Distinction between decompensation and stress hyperglycemia is often made or is not clear in many patients. However, treatment of the hyperglycemia along with the other problems improves outcomes.

In the inpatient, hyperglycemia may be defined as any blood glucose >140.[1] Hyperglycemia in the hospital may represent previous known diabetes, previous undiagnosed diabetes or hospital-related hyperglycemia. A review of the patient's previous records may indicate if the patient is indeed diabetic or if this is "stress-induced hyperglycemia." An HbA_{1C} may be useful in distinguishing stress-related hyperglycemia from previous unknown DM when conditions that interfere with A_{1C} measurements in the hospital including transfusions and hemolysis are excluded. Hypoglycemia is not uncommon in the hospital and is defined as glucose levels <70 mg/dL. Severe hypoglycemia is defined as a glucose level of <40 mg/dL.

Poorly controlled glucoses in the hospital may be associated with higher morbidity and mortality. Acute increases in the levels of glucoses have been shown to increase proinflammatory markers and cause endothelial dysfunction. In patients with acute MI, hyperglycemia *per se* increases mortality irrespective of whether they are diabetic or not. Patients admitted with MI and with admission glucoses >199 had a 44% 1-year mortality (vs. 19.3% when admission glucoses were <100). Known diabetics in this study had higher mortality rates (4%0 vs. 16%).[2] In addition, there is an association with increase in infarct size and with congestive heart failure.

Acute hyperglycemia is also associated with neuronal damage following brain ischemia. An increase in mortality is seen in hyperglycemic patients admitted for stroke. Observational studies suggest a threshold of glucoses greater than 110 and 130 as predictors of poorer outcomes. A doubling of blood glucose from 90 to 180 was shown to be associated with a 60% worsening of the penumbral salvage and a 56 cm^3 increase in the infarct size. Although the association between hyperglycemia and infection is less clear, a variety of abnormalities in the immune system and neutrophil function have been demonstrated with hyperglycemia. In surgical patients, hyperglycemia is a predictor of nosocomial infection.

Patients in medical and surgical procedures with new hyperglycemia have 18-fold increase in mortality; known diabetics in this series had a 2.7-fold increase in mortality when compared to normoglycemic patients. Hyperglycemic patients also had longer hospital stays and were more likely to require ICU admissions and also demonstrated a trend toward higher rate of infection and neurologic events.[3]

Control of glucose in the inpatient setting is associated with better outcomes. A significant body of evidence supports a direct role of insulin in these outcomes, suggesting potential anti-inflammatory and cardioprotective roles. Other studies attribute the benefits merely on better glucose control and the accompanying enhanced glycolysis and suppressed lipolysis.

There is a lack of randomized controlled trials (RCTs) that address specific targets for noncritical hospitalized patients. This being the situation, therapy should be aimed at keeping premeal glucoses <140 and random glucoses <180. Hypoglycemia defined as a glucose <70 in the hospital may be fatal and is more dangerous than hypoglycemia.[1] Glycemic targets and therapeutic strategy must focus on avoiding hypoglycemia most importantly; hypoglycemia remains the stumbling block for tight control in hospital settings.

There are no large studies that have investigated the potential role of various oral agents on outcomes in the hospital. Significant questions about the cardiovascular safety of sulfonylureas have been raised; however, there is insufficient data to specifically recommend against their use for this reason in this setting. Sulfonylureas, however, have other limitations in the inpatient setting. Long action and predisposition to hypoglycemia in patients not consuming normal nutrition are relative contraindications. In addition, they do not allow rapid changes in doses according to changing patient requirements. Metformin is an ideal oral hypoglycemic agent (OHA) in the outpatient setting. Specific contraindications limit its inpatient use, especially the risk of lactic acidosis. Although a recent Cochrane database review suggests that the risk of lactic acidosis with metformin may be lower than suggested, given the risk of hypoxia, hypoperfusion, and renal dysfunction in hospital settings, it seems to be prudent to eschew metformin in the inpatient setting. Thiazolidinediones increase intravascular volume in patients predisposed to cardiac heart failure and may cause increased endothelial permeability. Their cardiac safety is in serious question and they are, therefore, not ideal inpatient agents. Very little data are available on the role of dipeptidyl peptidase-IV (DPP-IV) inhibitors or the glucagon-like peptide-1 (GLP-1) agonists in the inpatient setting to make a recommendation.

Considering the numerous contraindications for oral agents in the hospital, insulin is clearly the preferred agent for inpatient glycemic control. When calculating insulin requirements, consideration of the following three issues is important:

- What is the basal insulin requirement? This is the amount of insulin required to prevent unchecked gluconeogenesis and ketogenesis.
- What is the nutritional insulin requirement? This is the insulin required to cover intravenous dextrose, total parenteral nutrition, enteral feedings, nutritional supplements or meals.
- What is the stress-related insulin requirement? This is a variable insulin requirement that accompanies acute illness due an increase in counter-regulatory hormones, stress, use of corticosteroids, pressors, etc.

In the ICU, intravenous infusion is preferred. In other settings, subcutaneous insulin is preferred. The preferred method would be to use a basal insulin (NPH or glargine or detemir) to provide basal insulin requirements with premeal nutritional supplementation with rapid action (regular insulin or lispro/aspart/glulisine). Other regimens could be equally effective, for instance, using analog mixtures thrice daily premeal. Supplemental insulin may be required based on the CBG. Sliding scale insulin is not recommended; it is potentially dangerous, can cause, and has been associated with, adverse outcomes in surgical patients. Modification of insulin dose is recommended when glucoses are <70 unless they can be explained, for instance, due to a missed meal. Capillary blood glucose meters are sufficiently accurate to guide care in the hospital.

Enteral nutrition commonly causes hyperglycemia. The use of basal insulin with on-demand short-acting insulin has been found to be useful.[1] Hyperglycemia is associated with increased mortality in patients on total parenteral nutrition.[2] Basal insulin, with on-demand short-acting insulin, usually meets patients' insulin requirements.

Patients may develop hypoglycemia for a variety of reasons in the hospital including a change in the nutrition, patients' access and ability to communicate needs, comorbidities, change in medications including corticosteroids, infection, sepsis and mismatched use of antidiabetic agents. Vigilance and use of modest targets and correct choice of insulin is required to prevent hypoglycemia.

Critique of Question 1

Correct Response: c

The patient has asthma requiring glucocorticoids. Glucocorticoids will cause hyperglycemia. OHAs will be insufficient to control these glucose fluctuations. In

addition, metformin will increase the risk of lactic acidosis, especially if radiologic or other procedures are performed although the risk of MF causing lactic acidosis has been downgraded by recent reviews of the data. In this setting, insulin is the best therapeutic option. A basal insulin with premeal short-acting insulin is ideally suited for this purpose. Supplemental insulin may be required at meals. Sliding scale insulin can be dangerous and best avoided. Although thiazolidinediones have been demonstrated to be effective in glucocorticoid-induced hyperglycemia, this is not true in a hospital environment.

Clinical Summary for Practice

Hyperglycemia defined as any glucose value >140 in the hospital requires therapy. Long-acting sulfonylureas, metformin, and thiazolidinediones are inappropriate for use in the hospitalized patient. Basal and premeal insulin with supplemental on-demand insulin is preferred for most of the patients.

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Section 2. Transitioning to Home Care

Question 2

A 62-year-old man was admitted for a community-acquired pneumonia 5 days ago. He is not a known diabetic. During the hospitalization, he was found to have blood glucose of 240. HbA_{1C} was 7.3. He was started on insulin. In the past 24 hours, his glucose levels are between 110 and 140 and he has required less than 4 units of insulin. He is now eating normally. What is the appropriate regimen for this patient at discharge?

(a) Lifestyle modification (LSM) only.

(b) Twice daily premixed insulin.

(c) Metformin 1 g at bedtime.

(d) Glibenclamide 5 mg b.i.d..

(e) Glimepiride 1 mg in the morning with bedtime glargine.

Discussion

Both over- and under-treatment of hyperglycemia are major concerns in hospitalized patients. The causes for this are summarized in Box 1. Hypoglycemia is of particular concern. It can occur spontaneously in patients with sepsis and is common in patients on several medications including quinolone group of antibiotics and β-adrenergic antagonists.[1–3] It is important to be proactive in order to prevent hypoglycemia with protocol-driven measurement of glucoses with appropriate orders for intervention when glucoses drop to less than 70 mg written in the case sheet. Identifying patients with advanced age, malnutrition, history of prior hypoglycemia, and autonomic liver and kidney disease as having high risk and flagging these patients appropriately is important. Daily reconciliation of medications is paramount. Nurses and other paramedical professionals must undergo adequate in-service training in the correct administration of insulin as well as recognition and management of hypoglycemia.

Capillary blood glucose testing with well-calibrated glucose meters is important. Most noncritical patients will benefit from premeal and bedtime measurement of glucose. Patients on parenteral nutrition should have CBGs done between 4 and 6 hours. Patients on intravenous insulin require more frequent measurement. CBG is sufficient in most situations. Errors are likely with falls in hemoglobin or with

Box 1. Risks for hyperglycemia and hypoglycemia in hospitalized patients
• Change in caloric intake including nil per oral status
• Medications including corticosteroids and vasopressors
• Failure to adjust therapy according to variations in glucoses
• Poor coordination between glucose measurements and insulin administration
• Use of sliding scales alone
• Communication issues, especially during transfer between services
• Use of long-acting sulfonylureas, especially in patients with renal dysfunction and the elderly
• Prescription, transcription, and administration errors

Adapted from Ref. 3.

perfusion. When glucoses do not match the clinical status, conventional blood glucose measurement in the lab is recommended.

It is important to plan a transition from the hospital to home. Recent hospitalization is a major risk factor for outpatient hypoglycemia.[4] Discharge planning, whenever possible, should start early. This should include transition to OHAs as required or moving to simpler regimens of insulins as feasible in a home situation. The hospitalization must be viewed as an opportunity to provide education to the patient and must include information about the disease itself, prevention of hypoglycemia, lifestyle changes, especially in view of the intercurrent illness that caused the hospitalization, prevention of hypoglycemia, self-monitoring of blood glucose, insulin administration, and medication. Communication should be established with the family and physician in the outpatient setting (if different) in order to establish a smooth transfer of care. It is desirable to set up a return outpatient visit within a month of discharge.[5]

Critique of Question 2

Correct Response: c

Hyperglycemia in hospital is an indication for therapy. An HbA_{1C} of 7.5 indicates that the patient did have diabetes at the time of admission. Most patients who are admitted with adequate A_{1C} can go back home on their home medications. This patient was drug naive. Insulin was used during hospitalization. Transition to OHAs is appropriate for this patient. Twice daily insulin or insulin and glimepiride may

increase the risk of hypoglycemia. Glibenclamide is not a suitable monotherapy for most patients with diabetes. LSM alone is not sufficient to reduce hyperglycemia when the HbA_{1C} is >7. Metformin is safe and effective in patients with mild hyperglycemia. It is important to ensure adequate follow-up and education prior to discharge.

Clinical Summary for Practice

Prevention of hypoglycemia in hospital is important. Concomitant conditions including sepsis and antibiotics may increase the risk for hypoglycemia. Patients at an increased risk must be identified and flagged. Nurses and other healthcare workers must be trained in recognizing and treating hypoglycemia. Premeal and bedtime CBG is sufficient to monitor in-hospital glucoses in most of the patients. Early discharge planning and recognition of the hospital stay as an opportunity to educate patients about diabetes is imperative. All patients must have a follow-up plan with a return visit to their doctors clearly determined as part of discharge advice.

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Practice Box

1. Assess glycemic control, coexisting comorbid conditions including renal function, caloric restriction including NPO and glucocorticoid use.
2. Stop long-acting sulfonylureas and metformin. Thiazolidinediones are not recommended if fluid overload is an issue.
3. Insulin is the safest. Basal insulin with premeal short-acting insulin with supplemental insulin on demand is the best option.
4. Sliding scale insulin is not recommended.
5. Premeal and bedtime monitoring with CBG is sufficient for most of the patients. Lab measurements are required only if CBG is suspected.
6. Glucoses between 120 and 140 are ideal. Glucoses >180 or <70 must be avoided.
7. Discharge planning should include transition to a stable regimen and education.

CHAPTER 17

Diabetes in the Intensive Care Unit

KM Prasanna Kumar, Harish Kumar

Section 1. Hyperglycemia in the ICU

Question 1

A 65-year-old man, known diabetic for the last 5 years, is admitted for a community-acquired pneumonia to the ICU. He is hypoxic and ventilated and is on enteral feeds. He is a diabetic on glimepiride 2 mg daily and metformin 1 g at bedtime as an outpatient. In the ICU, his glucoses level ranges between 260 and 300. Serum creatinine is 1.8 and HBA_{1C} is 8.4%,Which one of the following is the most appropriate regarding glycemic control?

(a) Switch to subcutaneous insulin by sliding scale.

(b) Switch to intravenous short-acting insulin analogue by infusion titrated to a glucose of 160–200.

(c) Switch to intravenous regular insulin by infusion titrated to a glucose of 140–180.

(d) Stop OHAs and add basal insulin.

Discussion

People with diabetes are hospitalized more often and for longer duration than those without diabetes,[1] for either medical or surgical conditions. Hyperglycemia in hospitalized patients leads to a poor outcome, in both diabetics and nondiabetics.[2–5]

Although observational studies link hyperglycemia to poor outcome, interventional studies with intervention to normalize glycaemia have yielded inconsistent results. Recent clinical trials in critically ill patients have either shown no benefit or increased mortality with tight control.[6–8] Moreover, the risk of hypoglycemia and its accompanying morbidity and mortality appears to be significant.[6–11]

When an intensive glucose control with intravenous insulin, targeting an arterial glucose of 80–110, was implemented in a surgical ICU, this resulted in a significant reduction in mortality.[2] When the same protocol was implemented in 1200 patients in the medical ICU by the same investigators, there was a decreased morbidity but an increased mortality.[10] There was a sixfold increase in hypoglycemia in the intensively treated arm and it was identified as an independent predictor of mortality. Similarly, efforts to recreate the favorable outcomes, seen in the DIGAMI trial,[3] have been largely unsuccessful. Two large studies showed no decrease in mortality with tight glycemic control following a myocardial infarction. One of them, however, showed a decrease in congestive heart failure and re-infarction in 3 months. In other critically ill patients, due to a multitude of causes, hyperglycemia >200 was associated with a 2.2-fold increase in mortality[12] but this has not been consistently reported in other studies.

On the basis of available evidence, insulin infusion should be used to control hyperglycemia in the majority of critically ill patients in the ICU setting, with a starting threshold of no higher than 180 mg/dL.[13] Once intravenous insulin therapy has been initiated, the glucose level should be maintained between 140 and 180 mg/dL. Greater benefit may be realized at the lower end of this range. Although strong evidence is lacking, somewhat lower glucose targets may be appropriate in selected patients. Targets <110 mg/dL, however, are not recommended.

Continuous intravenous insulin infusion has been shown to be the most effective method for achieving specific glycemic targets.[5] Because of the very short half-life of circulating insulin, intravenous delivery allows rapid dosing adjustments to address alterations in the status of patients. Only crystalline insulin is approved for intravenous use. There is no advantage in using lispro or aspart in an infusion. During intravenous insulin infusion used to control hyperglycemic crises, hypoglycemia (if it occurs) is short-lived, whereas in the same clinical settings, repeated administration of subcutaneous insulin may result in "stacking" of the effect of insulin, causing protracted hypoglycemia. Insulin infusion also appears to have anti-inflammatory effects. It is preferable to use well-validated protocols that are available or short of it , each institution have its own policy or protocol based on local availability of resources and expertise and what is locally possible

and practical. Patients who receive intravenous insulin infusions will usually require transition to subcutaneously administered insulin when they begin eating regular meals or are transferred to lower intensity care. Higher glucose targets are acceptable in terminally ill patients and in patients where close glucose monitoring is not feasible.

Typically, a percentage (usually 75–80%) of the total daily intravenous infusion dose is proportionately divided into basal and prandial components (see Chapter 16). Importantly, subcutaneously administered insulin must be given 1–4 hours before discontinuation of intravenous insulin therapy to prevent hyperglycemia.

Hypoglycemia is the major concern in the ICU which must be proactively sought and prevented by vigilant and educated ICU staff and strong medication error prevention programs. The American College of Physicians (ACP) recommends that in intensive care unit (ICU) settings, the usual target of IIT is normoglycemia (blood glucose level 80–110 mg/dL) and it does not recommend using intensive insulin therapy to normalize blood glucose in SICU/MICU patients with or without diabetes mellitus.[14]

Critique of Question 1

Correct Response: c

Sliding scale insulin, in which subcutaneous insulin is given based on capillary blood glucoses and a predetermined protocol, is dangerous and not recommended in critical and noncritical patients. Intravenous short-acting insulin analogues like lispro/glulisine/aspart has no advantage over regular insulin; regular insulin is preferred. A target of 140–180 is reasonable as this reduces the risk of hypoglycemia while avoiding significant hyperglycemia. There is a single study comparing GLP-1 infusion with intravenous insulin which shows that intravenous GLP-1 may be beneficial. There are no data with regard to exenatide which is not recommended at this time. Basal insulin is clearly useful in stable patients but is not appropriate in the critical care setting with varying glucose requirements.

Clinical Summary for Practice

Hyperglycemia is common in the ICU and can worsen outcomes. Intravenous insulin is the preferred therapy. Maintaining glucoses between 140 and 180 is considered optimal at this time. Avoidance of hypoglycemia is important.

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Practice Box

1. Intravenous regular insulin by infusion is preferred in critical care settings.
2. Use an infusion pump and titrate glucoses to a target of between 140 and 180.
3. Avoid hypoglycemia.
4. Give subcutaneous insulin prior to stopping intravenous insulin.

CHAPTER 18

Diabetes in Pregnancy

Krishnan Swaminathan, Sujeetha Damodaran, Ian Campbell

Section 1: Screening and Diagnosis of Gestational Diabetes Mellitus

Question 1

A 34-year-old primigravida with a family history of type 2 diabetes mellitus (T2DM), currently in the 28th week of gestation, has a 75 g oral glucose tolerance test. Results show a fasting glucose of 99 mg/dL, 1-hour value of 175 mg/dL and a 2-hour value of 156 mg/dL. Which one of the following statements is correct?

(a) She does not have gestational diabetes.

(b) She needs a HbA_{1C} to confirm the diagnosis.

(c) She has gestational diabetes and there is no need for further testing.

(d) She needs a 100 g oral glucose tolerance test on a different day.

Discussion

Pregnancy is a state of insulin resistance driven largely by the placental secretion of an array of diabetogenic hormones including growth hormone, human placental lactogen, progesterone, and corticotrophin-releasing hormone. These physiological changes are a double-edged sword, ensuring ample supply of nutrients to the fetus but at the same time increasing the risk of hyperglycemia in susceptible mothers.

Several adverse outcomes have been associated with hyperglycemia in pregnancy including pre-eclampsia, hydramnios, macrosomia, operative delivery, perinatal mortality, neonatal metabolic and respiratory complications.

The only non-controversial aspect of gestational diabetes mellitus (GDM) is the number of controversies in every area of screening, diagnosis, and management! There should be no controversy in India regarding whom to screen; universal screening of all pregnant women should be the norm, as we are a high-risk ethnic group. There are multiple international criteria for GDM. For all practical purposes, physicians and obstetricians in India have to choose between two sets of diagnostic criteria.

The Diabetes in Pregnancy Study Group India (DIPSI) guidelines recommend a 75-g glucose load irrespective of the time of last meal when the mother walks to the antenatal clinic, followed by a venous blood sample at 2 hours. GDM is diagnosed if 2-hour plasma glucose is ≥140 mg/dL. The study group recommends screening at 24–28 weeks gestation. However, due to the possibility of missing pre-existing T2DM, this group recommends early 1st trimester screening. If the 2-hour value is >200 mg/dL, she has overt diabetes detected during pregnancy.

The authors personally use the IADPSG criteria (International Association of Diabetes and Pregnancy Study Group) for diagnosis of GDM or overt diabetes. All women in their first pre-natal visit will have fasting or random plasma glucose and a HbA_{1C}. A fasting glucose ≥126 mg/dL or random glucose ≥200 mg/dL or a HbA_{1C}≥6.5% is diagnostic of overt diabetes. If fasting glucose <126 mg/dL but ≥92 mg/dL, a diagnosis of GDM is made. If fasting glucose <92 mg/dL, a 75-g OGTT is done at 24–28 weeks gestation. On a 75-g OGTT, if one or more value equals or exceeds the following, a diagnosis of GDM is confirmed.

- Fasting ≥92 mg/dL
- One hour post-glucose load ≥180 mg/dL
- Two hour post-glucose load ≥153 mg/dL

It is important for physicians and obstetricians to memorize these numbers, as the cut-offs are derived from the landmark Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) Study, which suggested thresholds at which odds for birth weight >90th percentiles were significant.[1]

The two-step approach of a 50-g glucose challenge test followed by a 100-g glucose tolerance test is still widely practiced in the United States but we personally believe that a one-step approach using a 75-g OGTT would be much easier in an Indian context.

Critique of Question 1

Correct Response: c

The lady in question has GDM based on the IADPSG guidelines. Two values exceed the thresholds following a 75-g glucose load (fasting glucose at 99 mg/dL and the 2-hour value at 156 mg/dL). She needs no further testing and should be diagnosed with GDM. The NICE guidelines (National Institute of Clinical Excellence, UK) recommend that HbA_{1C} should not be routinely used for assessing glycemic control or diagnosis in the second and the third trimesters.[2] However, HbA_{1C} along with a fasting or random glucose would be helpful in the first trimester especially at the first visit to exclude overt diabetes, as this may have implications in management.

Clinical Summary for Practice

- Universal screening for overt diabetes and GDM should be the norm in a high-risk population like ours
- Remember the numbers 92, 180 and 153 at fasting, 1 and 2 hours after a 75-g OGTT for diagnosis of GDM
- If one or more of the above values are equal or higher, a diagnosis of GDM is confirmed

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Section 2. Medical Management of Gestational Diabetes Mellitus

Question 2

The patient discussed in Section 1 was given diet and lifestyle advice. Regular capillary glucose monitoring showed fasting glucoses persistently around 95–100 mg/dL and 2-hour glucose between 130 and 150 mg/dL over the next 12 days. The next course of action would be (more than one response can be selected)

(a) Glucose targets are reasonable, she should continue with diet and lifestyle alone.

(b) Oral agents including metformin are absolutely contraindicated in pregnancy.

(c) Start 500 mg of metformin twice daily with a possibility of adding insulin if targets are unmet.

(d) Until sufficient evidence is accumulated insulin must be the only drug used. in pregnancy

Discussion

There is now enough evidence to suggest that treating GDM improves maternal and fetal outcomes. A recent systematic review and meta-analysis of five controlled trials and six cohort studies suggested that treating GDM results in less pre-eclampsia, macrosomia and shoulder dystocia.[1] Once a diagnosis of GDM is made, healthcare providers should strive for the following targets based on ADA and ACOG recommendations.

- Fasting glucose ≤ 95 mg/dL
- One hour post-prandial glucose ≤140 mg/dL
- Two hour post-prandial glucose ≤120 mg/dL

Based on these recommendations, patients require better control of glycemic targets to prevent complications. There is no raging controversy over the role of medical nutritional therapy (MNT) and a program of moderate exercise assuming no contraindications, even though there is scant level 1 evidence for both. Insulin has always been the gold standard in pregnancy due to its efficacy and the fact that it does not cross the placenta. But there has always been a huge debate about the role of oral agents, especially metformin use in pregnancy.

Intuitively, metformin in diabetic pregnancy is an attractive option as it reduces insulin resistance, has minimal risk of hypoglycemia, cost-effective, and much preferable than injections. However, there are legitimate concerns regarding metformin use in pregnancy as this drug readily crosses the placenta, raising concerns regarding congenital anomalies and long-term risks to the offspring. The MiG Study (Metformin versus Insulin for the treatment of Gestational Diabetes) has gone some way in addressing this issue. This was a randomized trial involving 751 women with GDM comparing metformin versus insulin. Reassuringly, neonatal complications or maternal hypertensive complications did not significantly differ between metformin and insulin groups. More women preferred metformin to insulin. Supplemental insulin was needed in 46.3% in the metformin group. It is also reassuring to note that "metformin babies" born to mothers with polycystic ovarian syndrome (PCOS) taking this medication throughout pregnancy showed normal growth and motor development at 18 months. More importantly, metformin may have beneficial effects on children exposed to this drug in utero. The MiG TOFU study followed up babies born to women in the MiG trial at 2 years of age. Children exposed to metformin had a larger measures of subcutaneous fat at 2 years raising the possibility of more insulin sensitivity later in life, though this is a mere hypothesis. The authors of this chapter have published work on metformin use in GDM and are comfortable using metformin in GDM if dietary measures fail, after detailed counseling to the woman and her family. There is some evidence behind glibenclamide use in GDM but we do not have any personal experience to recommend its use one way or the other.

However, it must be emphasized that metformin use is controversial. There is a transatlantic divide with American Associations advising caution and British Guidelines being more liberal with metformin use in pregnancy. One undeniable fact is that insulin is the gold standard in pregnancy and proven to be safe. Human regular insulin and human NPH insulins (isophane) can be used as a part of multiple injection regime in GDM. In terms of insulin analogues, insulin lispro and aspart have been investigated in pregnancy and shown to have acceptable safety profiles, no evidence of teratogenesis and minimal transplacental transfer. Insulin detemir can be used now based on a 2012 multinational study on the safety and efficacy of determir use in women with type 1 diabetes (US FDA has reclassified insulin detemir to Category B from C in pregnancy). Evidence for insulin glargine and insulin glulisine remains weak at this point of time. Any insulin regimen requires regular glucose monitoring and self-adjustment of insulin doses based on the numbers. The insulin regimen has to be individualized. For example, if the fasting glucoses are above targets, then either an intermediate acting NPH insulin

or insulin detemir can be started at bed time in doses of 0.1–0.2 units/kg based on the degree of hyperglycemia. If post-prandial glucose levels are above targets, then human regular insulin, insulin lispro or aspart can be started with gradual dose titration. If both fasting and post-prandial levels are elevated, we prefer a basal bolus four times a day insulin regimen as opposed to twice daily pre-mix insulin, as there is some evidence that glycemic control and perinatal outcomes are better with four times a day regime. Twice daily pre-mix insulins may be suitable in certain circumstances where convenience and cost concerns predominate.

Critique of Question 2

Correct Response: d or c

This woman has not clearly met the glycemic targets in spite of dietetic measures. Therefore, simply observing further is not an option. There is increasing evidence for metformin use in pregnancy. So, we would disagree with the statement that metformin is absolutely contra-indicated in pregnancy. However, there is definitely merit in those who are not comfortable using metformin in pregnancy till more evidence emerges. Insulin has been proven to be safe and effective. Therefore, **d** would be the first choice answer. We also believe that option **c** is a reasonable option based on evidence till date and our personal experience.

Clinical Summary for Practice

- Remember pregnancy glucose targets of <95, 140 and 120 for fasting, 1 hour and 2 hour post-prandial values, respectively.
- Insulin is the gold standard treatment to reduce hyperglycemia in pregnancy.
- There is accumulating evidence for the safety and efficacy of metformin use in pregnancy.

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Section 3. Obstetric Management

Question 3

The patient discussed in Section 1 is now at 35 weeks gestation. She is on insulin and metformin for glycemic targets. Her recent ultrasound scan at 34 weeks gestation shows appropriate estimated fetal weight and amniotic fluid volume. The mother is worried about the mode and timing of delivery. She is also concerned about neonatal complications and need for diabetes treatment post-partum. Which of the following statements is true?

(a) She can be advised normal delivery at 40–41 weeks gestation.

(b) She needs elective caesarean section at 36 weeks.

(c) It would be reasonable to contemplate elective delivery by 38–39 weeks if further progression is uncomplicated.

(d) After delivery, glucose levels return to normal and there is no need for further follow-up.

Discussion

The optimal timing of delivery in GDM has not been evaluated in well-designed clinical trials. In the absence of high-quality evidence-based recommendations, we have to be guided by international guidelines, published papers and personal experience.

In a nutshell, if the woman has diet-controlled GDM with normal metabolic, maternal and fetal parameters, there is no reason to expedite delivery before 40 weeks. In women with uncomplicated insulin-requiring GDM, delivery should be contemplated at 38 weeks.[1,2] In both the referenced studies, there was an increased prevalence of shoulder dystocia in mothers who were assigned to the expectant management group compared to those who were electively induced at 38–39 weeks gestation. There was no increase in caesarean section rates in the actively induced group in both the studies. Moreover, the prevalence of large for gestational age infants was much higher in the expectant management group. If there are concomitant medical condition like hypertension, preeclampsia or poor glycemic control is present, then delivery should be undertaken based on the discretion of the consulting obstetrician.

Caesarean section is not routinely indicated in all diabetic pregnancies. However, women with diabetes have a higher rate of caesarean section even after controlling

for confounding factors. At the time of writing, we are not aware of any Indian specific guidelines on the indications for caesarean section based on fetal weight. The ACOG practice bulletin (2013) suggests that scheduled caesarean section should be an option for women with GDM and an estimated fetal weight ≥4500 g. One caveat to be borne in mind is the fact that the average birth weight in India is lower compared to a Caucasian population and an appropriate approximation for this population must be done when making decisions. Additional factors like risks for shoulder dystocia, (non) progression of labor, concomitant medical conditions and past obstetric history should be considered at lesser fetal weights.

Most women revert to normoglycemia after delivery, as the diabetogenic effects of the fetus and placenta dissipate rapidly. A small proportion of women with GDM may have undiagnosed diabetes. Therefore, the authors suggest monitoring for 24–48 hours after delivery. If glucose parameters are within normal range, we suggest discontinuation of glucose monitoring. All women should be actively counseled to come back in 6 weeks for a 75-g OGTT as there is always the risk of persisting IGT or type 2 diabetes. It is also vital to discuss in detail about contraception and future pregnancies both at the time of discharge and follow-up visits.

Critique of Question 3

Correct Response: c

Since this patient is on pharmacological treatment, it would be reasonable to contemplate elective delivery by 38–39 weeks rather than continuing expectant management till 40 weeks due to reasons outlined in the Discussion section. There is no reason for an elective caesarean section at 36 weeks as the pregnancy is progressing normally. The woman in question should have detailed counseling regarding the risks of future diabetes at the time of discharge with plans for a 6 week 75 g OGTT.

Clinical Summary for Practice

- Optimal timing for delivery in women with GDM is not clearly defined.
- It would be reasonable to contemplate elective delivery between 38 and 39 weeks in insulin requiring women with GDM and no other complications.
- All women with GDM need a follow-up 75 g OGTT 6–8 weeks post-delivery.

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Practice Box

1. Universal screening for GDM should be the norm in a high-risk population like ours
2. Use any of the national or international criteria but use a criteria consistently for diagnosis of GDM
3. Authors preferably use the IADPSG criteria for diagnosis of GDM, remember glucose values of 92, 180, 153 at 0, 1 and 2 hours for diagnosis
4. It is worth treating GDM
5. Remember the targets <95, 140 and 120 during treatment of GDM at fasting, 1- and 2 hours post-prandial
6. Insulin is the gold standard treatment if diet and exercise fail to control targets
7. Human insulins, lispro, aspart and determir can be safely used in pregnancy; evidence for glulisine and glargine are weak at this point
8. There is increasing evidence for the safety of metformin use in GDM both in mothers and babies
9. If you are comfortable, use it after counseling the patient, if you are not, insulin is always there
10. All women should be counseled about the need for follow up 75-g OGTT after delivery and the need to continue lifestyle measures

CHAPTER 19

Hypoglycemia in Diabetes

GR Sridhar

Section 1. Preventing Future Hypoglycemia in Diabetes Patients

Question 1

A 58-year-old man with diabetes, under fair glycemic control, complains of frequent sweating and palpitations. He also complains of feeling unusually hungry and unable to tolerate hunger for more than a few hours. A few days ago, he delayed his meal by 2 hours and felt faint, which improved on eating sweetened milk. He has had diabetes for seven years, which is being managed with glibenclamide 5 mg t.i.d. Physical examination is unremarkable. FBS is 130; 2hPP is 190; HbA1c is 7.8; and serum creatinine is 2.2 mg/dl. Which one of the following is the most appropriate next step in preventing future hypoglycemia in this patient?

(a) Add a mid-morning and mid-afternoon snack.

(b) Admit for evaluation for insulinoma.

(c) Substitute metformin for glibenclamide.

(d) Teach family how to use glucagon injections.

(e) Substitute gliptin for glibenclamide.

Discussion

If it were not for hypoglycemia, diabetes mellitus would have been the simplest of diseases to treat—there are a variety of drugs to lower glucose levels, with more in the pipeline. Compelling evidence exists that normal glucose levels lower the risk of developing diabetes-related vascular complications. But there is a hitch; glucose lowering drugs do not know where to stop. Consequently, efforts to avoid elevated glucose levels are associated with the risk of lower glucose levels tethering on the dangerous hypoglycemia.

What Maintains Glucose Levels?

Normally, glucose is kept in a normal narrow range by the interplay of many chemical and hormonal systems. In diabetes mellitus, some of the components are impaired, which are replaced from the outside (insulin, drugs which stimulate insulin release). The replacement is coarse and is not governed by the time-to-time regulation which occurs in the body. One tries to match the energy intake and expenditure with the externally administered medications. In general care, the match between the two sides is crude.[1]

How Common is Hypoglycemia?

One of the largest population based-data on hypoglycemia published by Donnelly reported that among insulin-treated subjects with type 1 diabetes mellitus (T1DM), incidence of severe hypoglycemia was 115 episodes per 100 patient years, compared to type 2 diabetes mellitus (T2DM) who had 35 episodes per 100 patient years.[2]

Is hypoglycemia fatal?Unrecognized and untreated, hypoglycemia is potentially fatal. More importantly, hypoglycemia results in recurrent discomfort of fear of hypoglycemia, which can form a barrier to improved glycemic control. In the ACCORD trial, there was a higher incidence of death in the group which had higher hypoglycemia. But it was unclear if hypoglycemia itself was a proximal cause of cardiovascular events. Hypoglycemia is known, however, to be arrhythmogenic.[3]

What Prevents Hypoglycemia?

Normal physiology maintains glucose level in a specified (normal) range. Once plasma glucose drops, insulin secretion is immediately reduced, which stimulates glucose production from liver and kidney. Next, neuroendocrine stimulation releases

glucagon from the beta cells of pancreas, and epinephrine from adrenal medulla. Both in unison stop further glucose fall by stimulating glucose production from liver and kidney, and by reducing glucose utilization by peripheral tissues.

Impaired Defenses against Hypoglycemia in Diabetes

The coordinated glycemic regulation found in normal persons is impaired in diabetes mellitus. Often glucose-lowering drugs (e.g. insulin and sulfonylureas) act regardless of the ambient glucose level. Therefore, it is imperative that glucose in the form of food is taken at the appropriate time in order to match action of antidiabetic drugs. In addition, T1DM is associated with impaired glucagon which normally prevents hypoglycemia. Other abnormalities include a blunted epinephrine release, which warns against hypoglycemia in association with autonomic dysfunction.[3]

How to Identify Hypoglycemia: Whipple's Triad

The only way to diagnose hypoglycemia is by measuring plasma or capillary glucose and establishing the level is low. Symptoms are guideposts, but measurement of glucose is confirmatory. Whipple's triad is the name given to "(a) symptoms, signs, or both consistent with hypoglycemia, (b) a low measured plasma glucose concentration, and (c) resolution of these symptoms and signs after plasma glucose concentration is raised."

Adrenergic neurogenic symptoms are triggered by the sympathetic activation following perception of hypoglycemia.

Neuroglycopenic symptoms result from direct brain glucose deprivation and include behavioral abnormalities, proceeding to seizures and coma.

Predisposing Factors

Essentially hypoglycemia results when there is a mismatch between the glucose level and circulating insulin. Although normal persons have a precise relation among all variables, in diabetes, it depends on the individual to attempt such a balance. Since insulin or oral antidiabetic drug action cannot be terminated at will, the risk of hypoglycemia is real. Predisposing factors to severe hypoglycemia in T2DM include long duration of insulin treatment, and attempts to achieve near-normal glycemia. Insulin usage, especially for a longer duration, is associated with hypoglycemia. Sulfonylureas alone or in combination with other OHAs or insulin are notorious for causing hypoglycemia. Drugs like glibenclamide were shown to be more prone to causing hypoglycemia than even older drugs like chlorpropamide. Even gliptins and

GLP-1 analogs which almost never cause hypoglycemia will cause hypoglycemia when combined with sulfonylureas (Box 1).

Poor Food Intake

Poor food intake may be the result of a delay or having no access to food. Precautions must be taken to avoid such situations. If a delay is anticipated, a snack must be taken a couple of hours before the delay, or the dose of the antidiabetic drug modified. Fine-tuning cannot be done on the go; it requires capillary glucose monitoring and a general idea of the needed change in dose, based on previous experience. One has to be aware of the need to eat food at the proper time; ideally, there must be a chaperone to keep track.

Similarly, illness or gastrointestinal dysmotility can result in poor intake. During illness, antidiabetic medicines may be taken. Poor appetite, vomiting, or intestinal hurry may lead to inadequate energy intake and hypoglycemia. In these conditions, one should either avoid or reduce the dose of medicines, or switch to a short-acting drug in the interim period.

Decreased Requirement

Sometimes, the 'usual' dose of antidiabetic medication may exceed the body's need at that point of time. This is particularly true when there has been a bout or period of exercise, which may improve the action of insulin or increase the rate, at which subcutaneously injected insulin is absorbed. Adequate precautions must be taken to either reduce the dose of drug or take extra calories in anticipation of such activity.

Rarely, associated diseases may lead to hypoglycemia; these include adrenal insufficiency and hypothyroidism.[4] When usual doses of antidiabetic medicines lead to hypoglycemic episodes in the absence of other predisposing factors, these uncommon associations must be considered and evaluated.[5] Renal failure (diabetic nephropathy) must be suspected in all diabetics with hypoglycemia. Alcohol abuse is another cause.

Iatrogenic Hypoglycemia

A wrong dose of insulin injection may be disastrous. In India, since both U100 and U40 insulin are available, it is possible that 100 iu/mL insulin is taken with a 40 u/mL insulin syringe if the patient or pharmacist is not vigilant. Patients must be educated

against such mistakes. Hypoglycemia may be induced by either taking more insulin than prescribed or by skipping food. Rarely, this may be done intentionally (factitious hypoglycemia)Identification can be difficult, and psychological counseling is required in such situations.

Identification and Diagnosis

Hypoglycemia is identified by measuring glucose level and not by symptoms alone, especially when recurrent. Weakness, sweating, giddiness, or excess hunger may also occur in other conditions such as hyperglycemia, fatigue, vertebrobasilar insufficiency, coronary artery insufficiency, perimenopausal flashes, or unrelated conditions. Although presumptive treatment of hypoglycemia may be offered, these possibilities must be kept in mind.

Adrenergic neurogenic symptoms include trembling, anxiety, nervousness, palpitation, sweating, dry mouth, and a feeling of hunger. Neuroglycopenic symptoms due to glucose deficiency at the level of the brain are more serious: abnormal mental state, irritability, difficulty in thinking and speaking, headache and seizures leading to coma.

Management

Patients should be educated to identify hypoglycemia. When symptomatic (see above), blood glucose should be measured; if it is less than 70 mg/dL, 15–20 g of carbohydrate should be eaten (e.g. fruit juice or biscuits), and glucose level checked after 15 minutes. If still low, they must take another 15–20 g of carbohydrates. Unless very low, direct glucose ingestion is best avoided. With neuroglycopenic symptoms, parental glucose infusion will be necessary. Fifty percent glucose is preferred followed by an infusion of 10% glucose. The infusion must be maintained until the effects of the drug are reasonably eliminated, especially in patients with sulfonylurea-induced hypoglycemia and renal failure.

Glucagon kits are available and can be injected by the family members.

Hypoglycemia Unawareness

In subjects with long-standing diabetes, warning symptoms of hypoglycemia are attenuated and the subject may not have the warning features and may go into neuroglycopenic stage. Careful balance of food intake and insulin must be maintained. A few weeks of hypoglycemia prevention (by maintaining glucose levels above normal) may re-establish awareness.[6]

Prevention of Hypoglycemia

Various strategies should be employed to minimize hypoglycemia by patient education and appropriate use of antidiabetic drugs, along with monitoring of glucose levels. When hypoglycemia occurs, it should be immediately identified and corrected.

Future Therapies

Efforts are on to minimize the risk of hypoglycemia while maintaining glycemic control by the use of newer insulin analogs, continuous subcutaneous insulin infusion, and by hypoglycemic alarms. ewly introduced modulators of the incretin system such as exnatide and liraglutide, when used alone have loer risk of causing hypoglycemia. They are more expensive than the older conventional drugs..

Hypoglycemia is an important issue in patients with both T1DM and T2DM. The healthcare team, the individual, and the family must be aware of its presentation, must be prepared to identify and properly treat it.

Critique of Question 1

Correct Response: e

A mid morning snack is a good option for most patients with hypoglycemia occurring a few hours after a meal but will not solve the problem of this patient with underlying renal dysfunction. Insulinoma is rare and need not be considered when other more obvious causes are clearly present. Metformin does not cause hypoglycemia but must be used with caution in renal dysfunction. The subject under discussion had an elevated serum creaatinine of 2.2 mg/dl for which he must be evaluated further. Teaching the family how to give glucagon is important for future episodes but it will not prevent hypoglycemia. In this patient, the use of sulfonylureas (especially glibenclamide) in the background of renal dysfunction is the proximate cause of hypoglycemia. Switching to a gliptin could prevent further episodes.

Clinical Summary for Practice

Hypoglycemia is common and unrecognized in diabetes; in most patients, it is the result of a mismatch between medications and an intake of meals. Other predisposing factors include renal dysfunction and adrenal insufficiency. Patient education is the key in prevention and recognition. Treatment should incorporate strategies to prevent hypoglycemia, and not to compromise on achieving euglycemia for fear of hypoglycemia.[7]

Box 1. Risk factors for hypoglycemia
• Decreased or delayed food intake
• Increased physical exercise
• Wrong injection/syringe use
• Alcohol abuse
• Associated conditions
• Diabetic nephropathy, renal insufficiency
• Hypothyroidism
• Adrenal insufficiency

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CHAPTER 20

Prevention and Management of the Diabetic Foot

Aravind Sosale, Bhavana Sosale

Section 1. Who Needs Foot Examination?

Question 1

A lady, aged 42 years, visits the clinic with type 2 diabetes mellitus (T2DM) of 6 months duration. Her HbA_{1c} is 6.8% with oral hypoglycemic agents. She is following the exercise and diet regimen advised. She feels healthy and has no complaints. She is a homemaker and spends on an average about 12–14 h per day indoors. She also visits the temple everyday for an hour. She never had a foot exam in the past and is comfortable spending a substantial amount of time everyday barefoot. Which of the following is the correct approach to this patient?

(a) She does not need a foot exam at this visit, nor does she need to worry about walking barefoot as she has been diagnosed to have diabetes only in the recent past.

(b) She is asymptomatic and hence a foot exam, daily foot care and footwear usage are not mandatory.

(c) She needs a foot exam at every clinic visit, but may continue to walk barefoot until she is diagnosed to have neuropathy.

(d) She needs to undergo a foot exam at every clinic visit and needs to be educated about daily foot care and footwear practices.

Discussion

Foot problems are a major cause of mortality and morbidity in patients with diabetes. Foot complications result in increased hospitalization and treatment burden, both financial and physical.

Most events which are responsible for precipitating a foot complication are largely preventable. Periodic examination for the identification of high-risk feet substantially reduces ulcers and amputations. Patient education on prophylactic foot care and footwear practices is pivotal to the management of diabetes. With more than 65 million patients with diabetes in India and numbers increasing each year, there are more feet to save.

Foot Examination

Why should this be performed?

Foot examination is done to identify "at risk" feet. Screening helps to risk categorize patients into those with minimal and high risk feet. "High-risk feet" patients are those with neuropathy/loss of protective sensation (LOPS), ischemia, foot deformities, and history of previous foot ulcers. Not only does this help in determining the preventive and monitoring strategies in a normal foot, but also aids in timely referral to a specialist in those with high-risk feet.

How often should a foot exam be performed?

The American Diabetes Association standard of care 2014 recommends an annual comprehensive foot exam for all patients with diabetes. It also recommends that visual inspection of the feet should be performed at each visit.[1] A patient with normal feet may be re-examined annually, and those with high-risk feet need to be re-examined at a frequency of 2–3 months or more by a specialist trained in podiatry. However, keeping in mind socioeconomic and cultural differences and loss to regular follow-up, a comprehensive foot exam at each clinic visit is prudent even for patients without any abnormality.

What is the ideal time to start performing a foot exam?

A comprehensive foot exam is mandatory at the diagnosis of diabetes. As diabetic neuropathy is mostly "pain free," deferring a foot exam will escalate the number of preventable foot problems, amputations and burden of treatment on the patient and the doctor.

What are the steps to be undertaken in performing a comprehensive foot evaluation?

(1) History of smoking, previous ulcers, amputations, claudication and symptoms of neuropathy need to be taken note of.

(2) Ask the patient to take off his/her footwear including socks.

(3) Inspect both feet thoroughly for abnormalities of the skin (redness, black discoloration, loss of hair, nail changes, signs of infection, calluses, fissures), fungal infection between the toes and structural abnormalities(loss of arches, clawing of toes, prominence of metatarsal heads), ulcers and previous amputations.

(4) Neuropathic evaluation comprises of tests to identify LOPS. This includes testing for touch using a 10-g monofilament and vibration using a 128-Hz tuning fork/vibratip. Temperature or pain using pin prick and the ankle reflex can also be tested.[2]

Testing of cutaneous touch perception using a monofilament. The patient is asked to close his eyes. The monofilament is placed at right angles to the skin and pressure is applied until it buckles. The patient is instructed to reply in the affirmative each time he perceives the sensation. The sites on the plantar surface that need to be tested are represented in Figure 1.

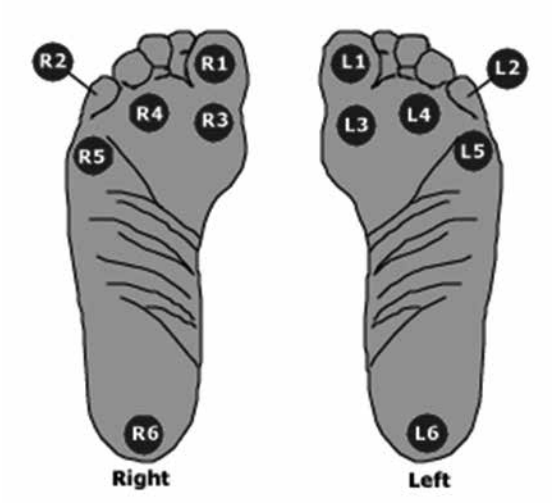

Figure 1.

Vibration testing using a 128-Hz tuning fork. The tuning fork is placed on the dorsum of the first interphalangeal joint. The patient is asked to report if he/she is able to perceive the vibration. A vibratip may also be used.

(5) Vascular evaluation includes assessment of the pulsations of the dorsalis pedis and posterior tibial arteries bilaterally. Measurement of the ankle brachial index is recommended for all patients with signs or symptoms of peripheral arterial disease (PAD). As more than 50% of the patients with PAD are asymptomatic, ADA (American Diabetes Association) recommends screening for all patients with one or more risk factors such as age >50, duration of diabetes >10 years, hypertension, dyslipidemia and smoking. An Ankle Brachial Index (ABI) 0.9–1.3 is considered normal.[1, 3]

What is the appropriate foot care advice that should be given to patients?

(1) Avoid tobacco use in any form.

(2) Examine your feet daily. Use a mirror or seek the help of a family member if you need to.

(3) Look for danger signs like redness, warmth, cuts, ulcers, swelling and discharge. Areas in between toes should also be examined for fungal infection.

(4) Wash your feet daily and wipe it dry.

(5) Never soak your feet in hot water.

(6) Cut your nails straight across and file sharp edges.

(7) Do not use any sharp instrument to remove corns or calluses. Report to your doctor.

(8) Never walk barefoot. It increases the risk of trauma and ulceration.

(9) Wear footwear indoors, inside your house.

(10) Use white socks, change socks every day and do not wear ones with a tight rim.

(11) Always look for foreign objects before putting on your shoes.

(12) Always buy footwear which are not tight or one size bigger than your feet size, with enough space for toes. Avoid high heels, shoes with rough seams. Wear closed footwear.

(13) If specialized footwear has been advised by your doctor, it is highly recommended that you use it.

What are the treatment options for patients with high-risk feet?

All patients with high-risk feet should be referred to a foot clinic with a surgeon trained in podiatry, a physician, a nurse, a nutritionist, a diabetes educator, and an orthotics team.

They need specialized footwear that offloads areas of high pressure to decrease the risk of ulceration. The management of patients with ulcers depends on whether the cause for ulceration is ischemia, neurological, or both. Investigations include glycated hemoglobin, renal functions, blood counts, appropriate cultures from wounds if there are any, x-rays, Doppler duplex scan, angiography, and plantar pressure measurements. Offloading, treatment of infection, wound care, revascularization, glycemic control, risk factor reduction, and rehabilitation form the various aspects of management. Although there are many therapies for better wound healing in a diabetic, analysis of evidence presents considerable difficulties in this field particularly as controlled studies are few and the majority are of poor methodological quality.[4]

Critique of Question 1

Correct Response: d

This patient needs a comprehensive foot exam as a part of the standard of care for a patient with T2DM. She also needs to be educated on daily prophylactic foot care and footwear practices that prevent foot complications. Reinforced education is the key to break away from long-standing traditional practices like barefoot walking indoors.

Clinical Summary for Practice

An annual comprehensive foot exam is recommended for all patients with diabetes. Education on accurate foot care and footwear practices is mandatory.

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Section 2.

Question 2

A 60-year-old man with T2DM for 10 years presents to the outpatient with an ulcer on his right foot since 2 months. His foot examination reveals a 2x2 cm bone deep ulcer at the base of the first metatarsal head. Purulent discharge is present. Sensations are absent in both feet and peripheral pulses are normal. Which of the following investigations would you order?

(a) HbA_{1C}, Pus culture, and sensitivity.

(b) HbA_{1C}, complete blood count with ESR, renal function tests, pus culture and sensitivity.

(c) HbA_{1C}, complete blood count with ESR, renal function tests, pus culture and sensitivity, foot x-ray, ABI index.

(d) HbA_{1C}, complete blood count with ESR, renal function tests, pus culture and sensitivity, foot x-ray.

Discussion

A patient with diabetes in his/her lifetime has a 25% chance of developing a foot ulcer.[1] Foot ulcers are a leading cause of amputations, mortality, morbidity, and decrease in quality of life and increase in healthcare costs. Management includes local wound care, treatment of infection, reperfusion, offloading, and glycemic control.[2,3]

What are the principles of wound care?

Wound care involves wound classification, assessment of the depth of the wound, examination for LOPS, evaluation of vascular status, and extent and severity of infection. The size and depth of the ulcer needs to be noted at every visit. All ulcers that probe to bone or present with underlying exposed bone should be assumed to have osteomyelitis unless proven otherwise. A foot x-ray should be ordered to look for osteomyelitic changes in all patients who present with nonhealing ulcers. These changes appear late on an x-ray and a normal x-ray does not rule out osteomyelitis. An MRI with elevated WBC counts and high ESR may clinch the diagnosis.[3]

The wound should be irrigated, debrided, and dressed by a surgeon. Debridement may be by the usage of sharps, proteolytic enzymes, or autolytic enzymes depending

on surgeon's choice. Mechanical debridement to remove necrotic tissue should be done by a surgeon with a scalpel except in cases of vascular compromise, where further increase in surface area of the wound can contribute to delayed healing due to ischemia. Biological debridement with medical grade maggots may also be practiced.[2,3]

The wound should be dressed regularly. Various dressings may be used based on the degree of necrosis and exudation. The dressing should be sterile, kept clean, and moist. They protect the wound, keep it moist, and promote healing. Care should be taken such that the dressing is not changed so frequently as to damage the surrounding healthy tissue. Dressings may be gauze moistened with saline, silver/antibiotic impregnated dressings, hydrogels, hydrocolloids, alginates.[4] Platelet-derived growth factors like becaplermin may fasten angiogenesis and healing. NPWT wound dressing (VAC) may be indicated in certain wounds to promote healing and decrease exudates.[5] Adjunctive therapies include HBOT (hyperbaric oxygen therapy) and use of G-CSF (granulocyte colony-stimulating factor).[4,6] Although there are many studies on type of dressing, local instillation of growth factors, hyperbaric oxygen or VAC, none of them have been based on large scale, randomized clinical trials. Wound bebridement, good glycemic control, control of infection, and offloading are the most effective therapy which helps in wound healing. One of the recent meta-analysis concluded that with the exception of HBOT and, possibly, negative pressure wound therapy, there is little published evidence to justify the use of newer therapies.

Human skin (i.e., a split skin graft, a full thickness graft) or biological engineered skin substitutes may be used as a graft in a granulating wound without infection.[7]

What are the components of infection control?

All ulcers with surrounding erythema, swelling, local rise of temperature, and purulent discharge are infected. Ulcers which are bone deep may have osteomyelitis. Lab reports such as an elevated WBC count, increased granulocyte count, raised ESR are indicative of infection. Bone involvement needs to be ruled out in all patients as it determines the duration of antibiotic therapy and surgical management (e.g., removal of the osteomyelitic bone fragment). A tissue curettage sample for culture/sensitivity needs to be sent from the base of the ulcer after debridement. This may be more accurate than a wound swab. Aspirates from abscesses should be analyzed for bacterial growth. In patients who present with bone deep ulcers, a bone biopsy (open or percutaneous) must be cultured to aid antibiotic therapy for osteomyelitis.[3]

The most common organisms causing infection are Gram-positive aerobes. Deep ulcers and extensively necrotic wounds may be infected with Gram-negative bacilli and anaerobes. Empirical antibiotic therapy to cover Gram-positive organisms must be initiated and appropriately changed based on culture reports. Frequent retrospective analysis of the organisms cultured in your hospital may aid to formulate an antibiotic algorithm for empiric coverage. If there is a suspicion of methicillin-resistant *Staphylococcus aureus* (MRSA) /infection with Gram-negative organisms, a second appropriate antibiotic may also be initiated. Most wounds are polymicrobial. Superficial wound swabs do not add value to treatment decisions as they often grow organisms that colonize the skin.[3]

Antibiotics may be administered orally for superficial ulcers. Deep ulcers, extensive necrosis, osteomyelitis, and sepsis are indications for intravenous antibiotics. Duration may range from 2 to 6 weeks or more if bone is involved. Duration of antibiotic therapy is a clinical decision that is taken based on the clinical condition of the wound and the patient.

What does assessment of vascularity include?

The peripheral pulses, that is, dorsalis pedis and posterior tibial artery, need to be felt. Even those with normal pulses may have asymptomatic peripheral vascular disease. Hence an ABI needs to be performed in all patients. An ABI of 0.9–1.3 is considered normal. Those with an abnormal ABI need to undergo a Doppler duplex imaging and must be referred to a vascular surgeon for revascularization (angioplasty or bypass grafting). Antiplatelets and statins in doses that aid cardiovascular risk reduction and medication to reduce claudication like cilastazole must be prescribed. This must be accompanied by strict glycemic control and blood pressure controlled to targets.[8]

How can one offload the foot?

Offloading devices include total contact casts, removable cast walkers, use of wheelchairs, crutches, absolute bed rest, and modifications in footwear. Customized shoes or insoles, wedge/half shoes or air shoes may be advised based on the individual patient. Evidence from clinical studies has shown that the best results are achieved with a total contact cast. This should not be used in patients with infection, osteomyelitis, heel ulcers, ischemia, and gangrene. The need for special expertise to apply the cast, difficulty in inspecting wounds in spite of a window, new ulcers resulting from ill-fitting casts, nonacceptance by patients are the challenges faced to use this mode of offloading.[2]

Critique of Question 2

Correct Response: c

HbA_{1C} estimation is necessary to assess the glycemic control. The severity of infection is determined by the clinical examination and by the total WBC count and ESR. Deterioration in renal function is indicative of acute renal failure and the glomerular filtration rate must be calculated to administer the renal safe doses of antimicrobials. A foot x-ray must be obtained to look for osteomyelitic changes. Pus/tissue curettage sample from the ulcer base must be analyzed for microbial growth and antimicrobial sensitivity patters to aid in targeted antibiotic therapy.

Clinical Summary for Practice

Glycemic control, wound care, control of infection, revascularization, and offloading are essential components in the successful management of a diabetic foot ulcer.

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CHAPTER 21

Psychosocial Aspects of Diabetes

GR Sridhar

Section 1. Managing Psychosocial Aspects of Diabetes

Question 1

A 36-year-old woman was diagnosed to have diabetes 3 years ago. She is married, with a 3-year-old child, a supportive family, and works in the BPO sector. Her job is secure; she exercises regularly and eats at home except when she is on night shift, which comes for 3 months every 270 days. Her body mass index is 24.2 and her metabolic parameters are under control with a drug combination of sulfonylurea and metformin. She kept her job despite an economic slowdown, while three of her colleagues lost theirs. She continued to be compliant to treatment. In the past two visits, however, she has gained 3.5 kg in weight, her glycosylated hemoglobin rose from 6.4% to 7.4% and her usually cyclic menstrual periods were delayed by 4 days in the past 2 months. Which one of the following would be the most appropriate next step in the management?

(a) Provide her with a pedometer to objectively assess whether she has been compliant with exercise.

(b) Add a thiazolidinedione.

(c) Evaluate her psychosocial status.

(d) Add basal insulin.

(e) Start an antidepressant.

Discussion

Managing diabetes mellitus is a multidisciplinary exercise, which requires coordination of the individual, her family and home life and office work. Outcomes are measured in terms of symptoms, signs, biochemical, and psychosocial parameters.

Technically any of the options above can be effective. Subjects underestimate their food intake and overestimate the physical exercise they perform. Beta-cell failure is progressive and additional drugs may be needed. In general, insulin is effective in controlling all degrees of hyperglycemia.

In this patient, there are many factors that make psychosocial intervention the desired first step in the management: being a woman with diabetes makes her vulnerable to greater psychosocial stress. She has to balance home, work, and a small child. Managing her diabetes imposes additional burden; she has been coping with it better than many by incorporating an exercise regimen, by compliance to medical interventions, and by achieving admiral outcome in her physical and biochemical results.

Potential sources of stress that could have acted included a shift duty although the cycle is changed every 90 days to allow the circadian rhythm to settle before the next change. Disturbed sleep is associated with impaired well-being resulting in obesity, insulin resistance, and hyperglycemia. A number of factors play in this such as frequent snacking of high-energy foods, and an imbalanced leptin/ghrelin ratio, leading to increased food ingestion.

The equilibrium was tilted by factors outside one's personal control: an economic slowdown impacts not only the cost of living, but also job security. She had increased workload to compensate for her colleagues' loss of their jobs. All these would contribute to stress leading to worsened glycemic control, weight gain, and ovulatory dysfunction.

Providing her a pedometer would have quantified her exercise; given her past compliance and the presence of precipitating factors, one does not have to immediately suspect compliance. On the contrary, the continuous reminder of step count may force her to increase her exercise to improve or at least keep with the 10,000 steps a day target.

Thiazolidinediones, although an effective add-on to drug hyporesponsiveness, are themselves associated with weight gain, and at least one drug is controversially

linked to adverse cardiovascular outcomes. Basal insulin, though effective, is associated with weight gain.

Although an antidepressant is a quick fix, it is probably important to establish if depression is present and then address its cause before using temporizing measures. In the given situation, an effective first step would be to evaluate her psychosocial status, provide her measures for coping, screen for depression, and treating it, if present.

Critique of Question 1

Correct Response: c

The logical cost-effective first step would be to evaluate her psychosocial status, provide her measures for coping, screen for depression and treating it, if present. See "Discussion" above for an elaboration.

Clinical Summary for Practice

Include evaluation and treatment of depression/psychosocial stress in management of diabetes, without losing track of physical and metabolic factors. Managing either could improve the outcome of the other, although evidenced-based information is yet to be obtained. National recommendations for psychosocial management of diabetes for patients from India are available.

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Section 2. Management of Depression in Diabetes

Question 2

A 72-year-old woman has type 2 diabetes. She is on saxagliptin 5 mg qd. She recently lost her son aged 50. In the past 4 months, she has been complaining of difficulty keeping up with life; her glycemic control has deteriorated. Her A_{1C} has climbed from 6.8 to 7.7 in the past 4 months. Which one of the following is the most appropriate next step?

(a) Add metformin 1 g at bedtime.

(b) Advice electroconvulsive therapy.

(c) Add nortriptyline 15 mg at bedtime.

(d) Add sertraline and recommend counseling.

(e) Add zolpidem 10 mg at bedtime.

Discussion

Up to 26% of patients with diabetes have varying degrees of depression.[1] Depression itself increases the risk of diabetes. In the diabetic, it increases the risk for persistent hyperglycemia. The elderly appear to be particularly vulnerable with up to a fivefold increase in mortality.[2] In addition, depression has profound psychosocial impact as was illustrated in the introductory case reducing quality of life, treatment adherence, reduced physical activity, and increased snacking. Depression, however, is underdiagnosed. A simple screening tool that should be used in patient encounters is outlined in Box 1. Once depression has been identified, it is important to seek appropriate help from mental health professionals. However, it is important for the primary physician to be continued to be involved in the care of the patient and not just transfer the "mental" part to another person.

Several modalities are useful in the diabetic patients with depression and need to be tailored depending on the patient, his or her environment, severity of depression, etc.

Cognitive behavioral therapy,[3] group counseling, and supportive psychotherapy have in small studies shown to improve depression and glycemic control. These

Box 1. Really short depression screening tool

- Depression screening tool (Patient Health Questionnaire, PHQ-2)
- Over the past 2 weeks, have you often been bothered by:
  - Little interest or pleasure in doing things? Yes/No
  - Feeling down, depressed, or hopeless? Yes/No
- *If the patient responds 'Yes' to either question, suspect depression; plan subject to a longer screening questionnaire (PHQ-9, a nine-item self-administered questionnaire.* Accessible on the web at*http://steppingup.washington.edu/keys/documents/phq-9.pdf.*

studies had methodological limitations which do not allow generalization. Clearly, however counseling-based therapies are useful in patients.

Only four randomized controlled trials have specifically looked at depression and diabetes; the use of nortriptyline was associated with an improved depression but deteriorating glucose control.[4] Fluoxetine demonstrated improvement in depression and a trend toward better glycemic control.[5] Sertraline in an extended randomized control trial was effective in providing remission and preventing relapses.[6] Glycemic control was somewhat improved.

A combination of psychological interpersonal and medical therapy appears to be superior and at least in one study there was a decrease in mortality in 5 years.[7]

Critique of Question 2

Correct Response: d

The patient has depression and this has probably reduced her compliance to OHAs. ECT is useful in patients who have suicidal ideations and must be only done by a trained mental health professional. Adding metformin is relatively contraindicated in a patient over 70 years of age and in this instance will not improve her glycemia. Nortriptyline has side effects which may worsen glycemic control, especially in the elderly. Zolpidem is an anxiolytic and may not particularly be useful other than improving sleep. A combination of interpersonal therapy and selective serotonin reuptake inhibitors (SSRIs) is the most effective.

Clinical Summary for Practice

Depression is common and worsens diabetes outcomes. Screening using a tool provided in Box 1 is a simple way to address depression. A combination of interpersonal therapies including cognitive-based therapies and pharmacotherapies including SSRIs appears to be the most effective. The existence of social strengths arising from social networks along with drug therapy can be effective in proper management of diabetes and depression.[8]

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CHAPTER 22

New Technologies in Diagnosis and Management of Diabetes

Jayashree Gopal

Section 1. Continuous Glucose Monitoring

Question 1

A 44-year-old man is diagnosed to have type 2 diabetes mellitus (T2DM) at the age of 33 years. He is currently on a short-acting insulin analog lispro 10 units before each meal, and glargine insulin 12 units at bedtime. He is regular with monitoring, and takes his meals regularly. Currently, his HbA_{1C} is 8.1%, and the other parameters are normal (no evidence for diabetic retinopathy; urine microalbumin is within normal limit; and serum creatinine and lipid profile are normal). His current complaint is that he seems to have frequent low blood sugars in the early morning 2–3 am, and also that he feels very hungry at around 5 pm. His SMBG readings are very variable, with FBS ranging from 54 to 274 mg/dL, and his 2-hour PPBS ranges from 160 to 240 mg/dL. His 5 pm blood sugar is around 150–160 most of the days. He is very frustrated that his FBS seems to follow no pattern consistently, and so he is unable to adjust night dose of insulin. He also wants to know why he feels hungry at 5 pm, even though his blood sugar is "normal." Which one of the following is the most appropriate next step?

(a) Change to twice daily premixed insulin.
(b) Stop glargine.
(c) Get serial measurements of 3 am glucose.
(d) Arrange for continuous glucose monitoring system (CGMS) for at least 3 days.
(e) Stop premeal boluses and add exenatide.

Discussion

The blood glucose at any point in time is affected by several different variables including, but not restricted to, the type of food, insulin dosage, exercise or level of physical activity, stress, time of the day, and the rate of nutrient absorption. One single glucose value does not tell us where in the glucose trend it is falling. For example, someone has checked their blood glucose at time point 2 (which is 250 mg/dL) in all three scenarios (Fig. 1). In series 1, the blood glucose is on an upward trend. In this situation, if adequate insulin is not taken, the next value may be excessively elevated. If on the other hand the scenario is like in series 2 (downward trend), higher dose of insulin may cause dangerous hypoglycemia. This is why trends are more important than single time values. Only CGMS is able to provide such data.

The other important data that CGMS can provide are that of mean amplitude of glycemic excursion (MAGE). This is found to be better correlated with acute oxidative stress, even more so than HbA_{1C} or postprandial glucose spike. Currently available monitoring and therapeutic modalities do not address the issue of maintaining blood glucose in the normal range, while avoiding extreme fluctuations both above and below the normal.

Continuous glucose monitoring system is an evolving technology that offers the user real-time information about their blood glucose. It should be differentiated from glucometers that provide a single time point value. The main advantage of CGMS is that the rate and direction of glucose change can be determined and

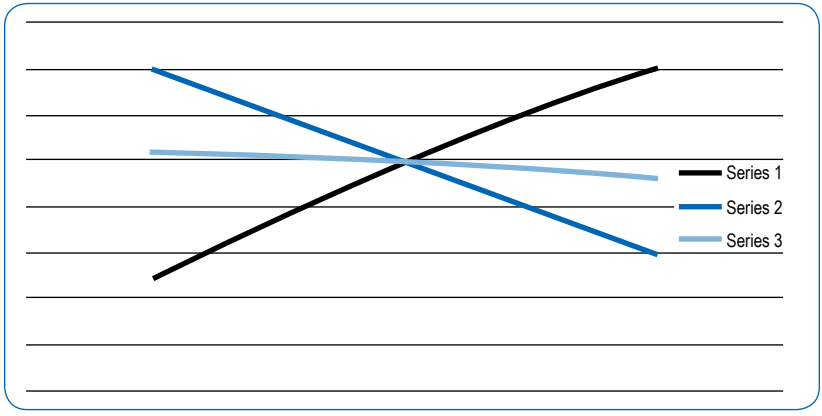

Fig. 1. Same glucose different trends

trends that lead to dangerous hypo- or hyperglycemia may be picked up. The procedure involves inserting a small plastic cannula subcutaneously (usually in the abdomen); this is the sensor that measures the amount of glucose in the interstitial fluid using the same amperometric technology used by traditional glucose meters. This value needs to be calibrated with the capillary blood glucose. For this reason, the traditional value with the glucometer also needs to be checked every 6 hours or so, while the user is wearing the CGMS. With earlier versions of the CGMS, the whole data needed to be downloaded to the computer every 24 hours or after 72 hours. So, it did not offer real-time values. The current technology is such that the values of the interstitial blood glucose can be seen on the monitor screen in real time. There is a lag between interstitial and blood glucose. At least in animals, there appears to be a correlation between interstitial glucose and CNS glucose.[1]

Who are likely candidates for CGMS? At present, due to cost and availability constraints, CGMS should be offered to all pediatric patients. Among adults, the technology may benefit those with type 1 diabetes mellitus (T1DM) who are not reaching goal HbA_{1C} despite the SMBG being at target, people who run higher blood sugars due to fear of hypoglycemia, those with hypoglycemia unawareness or frequent episodes of hypoglycemia. Patients and their families need to be highly motivated, and have a good understanding of physiology of glucose excursions and of the type of insulin and their effects. The need for SMBG, in addition to CGMS, should be recognized. There are a number of barriers existing today that prevent application of CGMS more widely. These include the following:

- Uncertainties about accuracy
- Cost
- Lack of adequate trained staff
- Need for specialized software and access to computers

However, in the proper scenario, CGMS can give the doctor and the patient useful information with respect to the following:[2]

- Direction of change of blood glucose
- Rate of change of glucose
- Rate of acceleration or deceleration
- Data can be used to make predictions of future trends

CGMS studies in type 2 diabetes patients have shown, for example, increased arrhythmias during nocturnal hypoglycemic episodes.[3] Increased glycemic variability is also increasingly being recognized as contributing to prognosis after an acute cardiac event (increased mean amplitude of glucose excursions is

associated with increased major adverse cardiac events following ST elevation myocardial infarction and intervention.[4]

Critique of Question 1

Correct Response: d

In a highly motivated patient such as this, switching from basal to premixed bolus is not indicated and will not improve outcomes. Stopping the basal insulin can be dangerous. In T1DM, 3 am glucoses may be useful in detecting Somogyi or Dawn phenomenon. This patient has symptoms at other times also. Adding exenatide will not help without first identifying the underlying problem. CGMS is the correct response.

Follow-up

The CGMS was worn by the patient for 4 days. It showed that he consistently had very low blood sugars between 12 midnight to 3 am, and that early morning high blood sugars seemed to be a reaction to this. This occurred in spite of the use of a long-acting insulin analog (glargine). It also showed that after lunch, his blood glucose went up to a maximum of 350 mg/dL 1 hour after lunch, had come down to 240 mg/dL by 2 hours, and then there was a relatively rapid fall between 2–3 hours from 250 or so to 100 mg/dL. This rapid fall in glucose triggered his feelings of hunger. He was counseled to split his lunch, and he found much less variability in blood glucose flux, and his feelings of hunger diminished to a large extent. The problem of early morning hypos persisted however, and for this reason, he was counseled on the use of an insulin pump.

Clinical Summary for Practice

Continuous glucose monitoring system is valuable in providing real-time trends of glucose. This will better help patients achieve targets and avoid dangerous hypoglycemia and wide fluctuations. However, this is still relatively new technology that is expensive and needs further validation before widespread use.

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Section 2. Insulin Pump

The patient in Section 1 will serve as the basis for discussion. A follow-up is provided at the end of the discussion.

Insulin Pump

This is a device that consists of an infusion pump to infuse insulin directly into the subcutaneous tissue. This is attached to a disposable plastic cannula, and has a disposable reservoir (similar to a cartridge in an insulin pen) of insulin. The disposable plastic cannula is self-inserted subcutaneously, and needs to be changed every 3–5 days. The advantage of using a pump to deliver insulin is that doses may be finely titrated. The insulin used is always short-acting insulin (regular or analog). As this is infused continuously, it does away with the need for basal insulin. There are a number of advantages of using an insulin pump [(therefore referred to as continuous subcutaneous insulin infusion (CSII)]. These include the following:[1]

- Significant reduction in episodes of hypoglycemia, particularly fasting hypoglycemia as seen in T1DM.
- Improvement in sexual function and peripheral neuropathy in T2DM.
- Overall improvement in HbA1c in both T1DM and T2DM in selected cases.
- Improved quality of life measures (probably due to smoothening out of the glucose fluxes).
- In some patients requiring extremely high doses of insulin, use of the CSII has led to a reduction in total daily insulin requirement.

The concerns with the use of the pump, mainly precipitation of diabetic ketoacidosis (DKA) or hypoglycemia due to inadvertent slipping out of the cannula, or excess bolus being given were mainly with the earlier generation of pumps. The current generation of pumps have relatively secure mechanisms. The main constraint against the use of the pumps is the cost. There is the initial cost of purchasing the pump, and a recurring cost every month. For people who can afford the pump, the flexibility in lifestyle that it offers makes it an attractive option. Emerging data support the use of CII in T2DM. The OpT2mise trial, a multi-centric, international trial reported that insulin pump gave better HbA_{1C} reduction as compared with multiple daily insulin injections in poorly controlled type 2 DM (the average reduction was 1.1% versus 0.4%, and there were 168 and 163 patients in each arm respectively.[2]

Some pumps are linked to the CGMS. This closes the insulin delivery loop. A recent study reported on the use of the sensor augmented pump compared with multiple daily doses of insulin; the incidence of hypoglycemia and weight gain was comparable in the two groups with much lower HbA_{1C} in the pump group.[3]

Newer features in pumpls such as threshold-suspend with sensor-augmented insulin-pump therapy, as compared with sensor-augmented insulin-pump therapy alone is able to reduce the risk of hypoglycaemia.[4] The use of Insulin and glucagon administered by a fully automated, bihormonal, bionic pancreas has been reported. The use of a bihormonal system was reported to improve glycemic control, with less hypoglycemic episodes.[5]

Clinical Summary for Practice

Continuous subcutaneous insulin infusion has a limited and selective role in patients with T2DM. With improvements in technology and closing of the loop, we could see an expansion of this technology in patients with T2DM requiring insulin.

Follow-up

The patient was initiated on an insulin pump. The basal dose of insulin could be adjusted such that minimal doses of insulin were infused at the time of the lowest blood sugars, as was revealed in the CGMS. Also, as he was asked to split his lunch, the pump was programmed to give bolus of insulin before the meals. Within 2 months, his HbA_{1C} reduced to 7.5%, his blood sugars were more stable (FBS 120–140 range), and he did not have the symptoms of hypoglycemia midevening.

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CHAPTER 23

Performance Improvement in Diabetes Care

Krishna G Seshadri, GR Sridhar

Section 1. Improving Diabetes Care

Question 1

A 38-year-old physician is in practice of diabetes for the past 12 years. He has clinic with the services of a nurse, a dietitian, and a junior physician. The clinic is in a 30-year-old building and has 2400 square feet with a provision for phlebotomy and EKG. It has a good reputation in the community. The clinic has an outpatient record system. Despite being successful, the physician feels that many of his patients are slipping through cracks. He attends CMEs regularly where there is an emphasis on achieving targets but feels that many of his patients are not achieving targets. He would like to improve his program. Which one of the following is the most appropriate next step?

(a) Improve the facilities of the building and modernize it.

(b) Hire a consultant to implement ISO.

(c) Hire a consultant to implement Joint Commission International Accreditation (JCIA) – primary care center status.

(d) Start or enroll in a performance improvement program.

(e) Do nothing. Do not argue with success.

Discussion

Evidence and guidelines constantly remind us about improved outcomes that occur by reaching goals of glycemia, BP control, etc. Real-world management tells us that though we would all like our patients to have an A_{1C} of <7 and a BP of 130/80, this seldom happens. There are many factors for this – societal, system-based, patient-based and our own clinical inertia.[1] Many experts feel that a system-based approach to improve performance in clinical care[2] allows physicians to make the right steps in the arduous journey towards excellence. In the developed world, there are many formal practice improvement programs available for physicians. It is necessary to assess the quality of care in clinical practice so that it can be used as a baseline in order to improve further.[1] The following seven-stepped approach may be useful to the novice who seeks to improve his performance. More formal avenues are available to institutional practitioners.

Know the Benchmarks of Current Care

Diabetes along with coronary artery disease (CAD) is one of the most protocol-driven diseases with fairly well-defined care pathways. Groups of experts and professional societies periodically review goals of care and publish them. The ADA publishes standards of care in diabetes annually. Other professional organizations including the American Association of Clinical Endocrinologists (AACE), National Institute for Clinical Excellence (NICE), and the European Association for the Study of Diabetes (EASD) periodically defined targets. At the time of standards of care, include (but not limited to) the following:

- Height, weight, and BMI at each visit
- Annual eye examination or ophthalmologic referral
- Annual foot examination
- BP measurement at every visit and BP <130/80 and use of ACE inhibitors/ARB for increased BP
- Annual flu vaccine
- Pneumococcal vaccine
- Periodic counseling on medical nutrition therapy (MNT)
- HbA_{1C} done twice a year and HbA_{1C} <
- LDL < 100 (<70 in established CAD) and statin use to reduce LDL to <10 as 0 or 30% of initial baseline

- Aspirin use in men over 50 (>40 and more than one risk factor), women over 60
- Documentation of microalbuminuria and use of ACE inhibitor, if appropriate

Assess your Current Practice

Once you are familiar with benchmarks, it is important to objectively assess your practice. A chart review that is done retrospectively or prospectively will help. If you are busy, choose a junior colleague to gather the data. Choose a list of simple parameters and some targets for future use. Box 1 lists the Healthcare Effectiveness Data and Information Set (HEDIS) measures for diabetes, which are used by over 90% of America's health plans to measure performance on service and healthcare. You do not have to review each file but a good representative sample that includes different age groups, both sexes, and different spectrum of care (new, older, multiple drugs, etc.) is important.

Once the data are gathered, tabulate it. A statistical study is not necessary. Raw percentages tell a fairly good story. Write down the results – for instance, 50% of my patients get a detailed foot examination annually, 20% of my patients have had a flu shot the last year, 50% of my patients have BP done each visit of which 60% have BP < 130/80, 60% of my patients have HbA_{1C} done twice the last year; 30% of them have A_{1C}s less than 7.

Box 1. HEDIS measures for diabetes[3]

HEDIS measures for comprehensive diabetes care estimate the percentage of members who had each of the following:

- A_{1C} screening
- Good A_{1C} control (A_{1C} < 8%; A_{1C} < 7% for a selected population)
- Poorly controlled A_{1C} (A_{1C} > 9)
- BP control to less than 130/80 mmHg
- BP control to less than 140/90 mmHg
- Eye examination
- LDL-C screening
- LDL-C controlled to less than 100 mg/dL
- Medical attention for nephropathy

Find out Where you Stand

Reviewing your results can be dismaying; do not fret. You can never be a 100% on target but need to be on the way to it. Knowing your data is meant to create a sense of urgency in improving yourself. It is useful to know how you are faring in comparison to your colleagues since it will help you set targets. Table 1 lists the HEDIS measures for commercial insurance providers in the US. National benchmarks have been established for many countries. You can compare yourself with them. If you have colleagues with whom you can create this program together and they are willing to share information with you, compare yourself with them.

Know Where you Want to Go

Once you have reviewed your data, it is usually evident what you need to do. Most changes required are simple enough. But it is important to make reasonable targets over short period of time. Choose simple targets first and tackle complex ones later. For example, if less than 50% of patients are having BP measured, its better to tackle it first than concentrating on getting everyone's BP down to target. Make a list. For example, at the end of 6 months in my practice, 80% of patients will have a BP measure at each visit (from 50%), 50% of patients will have a flu shot offered (from 20%), and 60% of all patient will be on a statin if indicated (from 20%).

Be realistic. Ensure that you have the time to make the changes that you plan. If you are busy and cannot choose less ambitious targets, get help.

Table 1. HEDIS measures for diabetes and compliance[3]

Measure	Commercial insurance
A_{1C} screening	89.2
A_{1C} control <7%	42.1
A_{1C} control <8%	61.6
Poor A_{1C} control >9%	28.2
BP control <130/80 mmHg	33.9
BP control <140/90 mmHg	65.1
LDL-C screening	85.0
LDL-C control <100 mg/dL	47.0
Eye exams	56.5
Medical attention for nephropathy	82.9

Make Changes

Once you have determined the targets set to work. Documentation is the key. If you do not have a good case record, create one. Ensure that a flow sheet is present in the front of the chart with your targets clearly written. A problem list is invaluable. Ensure that allergies are clearly documented in the chart. Charting using the SOAPE (Subjective, Objective, Analysis, Plan, Education) is useful in achieving goals. If possible, switch to an electronic medical record. There are many paid and some free ones, each of them constantly improving and many have built in reminders that allow you to achieve your target with each patient. One such free EMR is at www.practicefusion.com (requires an active net connection during entry).

It is important to involve all your team members make them aware of the targets, educate them and seek their support. Remember that patients are an important part of your team. Involve them in their care. Very often there is a perception difference in what we believe we have educated patients about and what they think we have done for them. This can be measured and corrected and when done is invaluable in improving care and achieving goals

Review your Performance

After the specified period, relook at your data. Look at where you have done well; see where you have done poorly. Analyze the reasons for your successes and celebrate them. Set the next higher target. Analyze the reasons for not doing well; is it a knowledge deficit on your part? Are systems not in place? Are your not educating patients well? Look at this carefully and make course corrections.

Start the Cycle Again

Set the bar higher and plunge in again. Note that this is a cycle, which means it is continuous. As you go higher you may want to participate in formal CQI programs – or even look for accreditation by the various agencies that offer it. Remember that accreditation is only a means to an end and not the end itself. Quality is a never-ending process, is a fiduciary commitment by the physician to help patients have better outcomes and better quality of life.

Critique of Question 1

Correct Response: d

Bricks mortar and fancy exteriors do not make a great institution – it is the people, the processes, commitment and values in it that make an institution

great. Modernization will improve facilities but necessarily outcomes. ISO is a process-driven program that may help improve quality but unless all members of a healthcare program are involved it only becomes a certificate quest and will not make an important impact on patient care. JCIAs measurables are patient driven, but they are only a means to an end and may not be suitable for most of the clinics in India like this one. Although we cannot argue with success, resting on your laurels does not help. This physician will be most benefitted from a simple practice improvement program as outlined above.

Clinical Summary for Practice

Performance improvement begins with knowing benchmarks and assessing current status. Identifying simple targets and making changes to reach those targets is the next step. Making small feasible changes to achieve the new targets is the next step. After the specified period is done, review performance and use the lessons learned to make new improvements. This performance improvement cycle is never ending and very rewarding.

References

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3. Titler MT. The evidence for evidence based practice implementation. The evidence for evidence-based practice implementation. In Hughes RG, Ed. *Patient Safety and Quality: An Evidence-based Handbook for Nurses, Vol. 1* (Chapter 7). Rockville, MD: Agency for Healthcare Research and Quality; 2008.

Practice Box

1. Know the benchmarks.
2. Assess your performance in the benchmarks through a chart review.
3. Compare your performance with national or other published numbers.
4. Set targets.
5. Implement changes.
6. Review performance.
7. Start over again.

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