2   Diabetes Mellitus Overview

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ABSTRACT

Diabetes mellitus, the most common metabolic disorder affecting the population, has many clinical and psychological implications for the patient. The provider must address these issues comprehensively. This chapter will describe the global burden and cost of diabetes mellitus, define its classifications and diagnosis criteria, detail its current treatment options, address associated complications including depression, fear of hypoglycemia, and fear of weight gain, suggest strategies for healthy lifestyle changes, and illustrate the importance of the patient's self-care and empowerment.

THE BURDEN: THE GROWING PROBLEM OF DIABETES MELLITUS

Diabetes mellitus is the most common metabolic disorder affecting humans and is characterized by chronic hyperglycemia. The prevalence of diabetes worldwide was recently estimated to be 171 million (2.8%) in 2000 and may rise to 366 million (4.4%) by 2030 *(1)*. There are two main types of diabetes – type 1 diabetes, which is caused by an autoimmune insulitis leading to an absolute deficiency of insulin, and type 2 diabetes, which usually includes a combination of insulin resistance and a β-cell secretory defect.

In recent years, the prevalence of type 2 diabetes, which accounts for approximately 90% of people with diabetes, has reached pandemic proportions *(1,2)*. The American Diabetes Association (ADA) estimates that 17.5 million people in the United States have been diagnosed with diabetes *(1)*. The lifetime risk of acquiring type 2 diabetes is approximately 50% in individuals with morbid obesity, an insulin resistance promoter *(3)*. Insulin resistance is a major pathophysiologic abnormality associated with type 2 diabetes that occurs initially in muscle tissue and later in the liver; it develops many years before the onset of hyperglycemia *(4)*. β cells within the pancreas initially compensate to maintain normal glucose metabolism by increasing the amount of insulin they secrete. Over time, the corporal demand for insulin exceeds the ability of the β cells to compensate, ultimately leading to pancreatic exhaustion and a major decline or halt in insulin secretion *(5)*. As insulin secretion declines there is usually a rise in postprandial glucose, which is then followed by a rise in fasting glucose. These increasing glucose concentrations further compromise insulin secretion and insulin action, a phenomenon called glucose toxicity *(4)*. Free fatty acids are also often elevated in individuals with uncontrolled type 2 diabetes; these also compromise insulin action and insulin secretion *(6)*.

More than 90% of individuals with type 1 diabetes develop this disorder as a result of autoimmune destruction of the β cells, a process which begins many years before the clinical onset of the disease. The precise mechanism precipitating the autoimmune process is not known. It is known, however, that antibodies to islet cell antigens and even insulin are present for years before overt hyperglycemia occurs *(4)*. Improvement of glucose control after presentation of the disease is often followed by a "honeymoon" phase, during which insulin requirements decrease for variable periods of time, only to be followed by further increases in insulin requirements as further β-cell destruction ensues *(7)*.

THE COST OF DIABETES MELLITUS

In 2007 the American Diabetes Association (ADA) estimated that the United States spent $174 billion in direct and indirect costs treating diabetes and its complications; this reflects an increase of 32% since only 2002. An estimated $116 billion is for medical expenditures, much resulting from treatment and hospitalization of people with diabetes-related complications. Approximately $58 billion is consumed by the indirect costs of the disease – reduced productivity of both those in the labor force and unpaid workers, unemployment from disease-related disability, and increased absenteeism. Approximately 1 out of every 5 healthcare dollars in the United States is spent on someone diagnosed with diabetes *(8)*.

In addition, diabetes claimed more than 284,000 lives in 2007 and remains the leading cause of blindness, end-stage renal disease, and non-traumatic lower limb amputations in the western world. Considering that an additional 6 million more people are believed to have diabetes but have not yet been diagnosed, the American Diabetes Association study estimates that the actual cost of diabetes may greatly exceed $174 billion *(8)*.

CLASSIFICATION AND DIAGNOSES

Type 1 DM

As outlined above, type 1 diabetes is characterized by β-cell destruction and leads to absolute insulin deficiency, either immune-mediated or idiopathic. It can occur at any age and presentation is usually acute. Symptoms indicative of type 1 include: polyuria, polydipsia, polyphagia, weight loss, blurred vision, recurrent vaginal or urinary tract infections, and fatigue. In older adults, type 1 may present more insidiously, similarly to type 2 diabetes, and is referred to as latent autoimmune diabetes of adults. Ninety percent of people with type 1 diabetes develop this as a result of autoimmune islet cell destruction, which is characterized by insulitis and the presence of antibodies against the β cell or insulin itself. All patients with type 1 diabetes eventually become insulin dependent *(7)*. Soon after initiation of insulin therapy in type 1 diabetes, some patients note a decline in insulin requirements.

Type 2 DM

The aging world population, increased prevalence of obesity, increased incidence of insulin resistance (mainly due to obesity), and a progressive decline in β-cell secretory function are the major factors that lead to hyperglycemia in patients who develop type 2 diabetes. This is a progressive disease, characterized by a progressive decline in insulin secretion, resulting in increasing

medication requirements and ultimately insulin treatment for many patients with this disorder. At the time of diagnosis it is estimated that 50% of β-cell function has been lost in individuals with type 2 diabetes *(7)*.

The most common complications associated with diabetes are macrovascular (e.g., coronary heart disease, peripheral vascular disease, and cerebrovascular disease) and microvascular (e.g., retinopathy, nephropathy, and neuropathy). Coronary heart disease accounts for more than 55% of deaths in patients with type 1 and type 2 diabetes and is the main cause of excess mortality in individuals with diabetes *(9)*. Despite laser treatment available to halt vision loss, diabetic retinopathy is very common and often results in blindness, accounting for 11% of new cases of blindness in the United States each year *(10)*.

Diabetic nephropathy accounts for entirely one-third of all cases of dialysis-requiring end-stage renal failure in the United States *(11)*. And though diabetic neuropathy is rarely a direct cause of death, it is a major cause of morbidity and a contributor to many circumstances that impact patients' quality of life *(12)*. Symptoms of peripheral neuropathy range from numbness to severe pain in the feet. A patient with neuropathy is more likely to develop ulceration of the feet. Ulceration in someone who also has coexistent peripheral vascular disease further increases risk for the development of gangrene and/or amputation. Diabetes is the leading cause of non-traumatic lower limb amputations in the world *(12)*. While microvascular complications are not the major cause of mortality in people with diabetes, they are a source of major concern amongst patients and contribute to the morbidity associated with the disease. Early detection and aggressive treatment of these chronic microvascular complications reduce morbidity and improve quality of life for people with diabetes.

Gestational Diabetes

Gestational diabetes is defined as diabetes developing or discovered during pregnancy. The associated risks of gestational diabetes are pre-natal morbidity and mortality as well as an increased rate of cesarean delivery and chronic hypertension in the mother *(13)*. Women with gestational diabetes are more likely to give birth to babies large in weight for gestational age (macrosomia) which is the reason why more women with gestational diabetes have cesarean deliveries. These infants are also more likely to develop hypoglycemia following delivery. Women with pre-existing diabetes who become pregnant are more likely to have infants with congenital malformations if their glycemic control is suboptimal during the first trimester of pregnancy. It is thus vitally important for all women with diabetes to be counseled about the risks of hyperglycemia and pregnancy prior to conception and for women with diabetes to plan their pregnancies so as to reduce the risk for congenital malformations in their offspring

(13). Up to 50% of women with gestational diabetes go on to develop type 2 diabetes within 5 years of diagnosis with gestational diabetes *(13)*.

Other Types of Diabetes

Other types of diabetes may be caused by a variety of factors, including but not limited to genetic defects in β-cell function, genetic defects in insulin action, diseases of the exocrine pancreas (such as cystic fibrosis), and can be drug or chemical induced (such as in the treatment of AIDS or after organ transplantation) *(7)*.

DIAGNOSIS

Clinically, diabetes is defined as the following: casual plasma glucose greater than or equal to 200 mg/dl with symptoms of diabetes including polyuria, poly-dipsia, ketoacidosis, and unexplained weight loss *OR* fasting plasma glucose greater than or equal to 126 mg/dl *OR* a result greater than or equal to 200 mg/dl 2 h following a standard 75 g oral glucose tolerance test *(14)*. The distinction between type 1 and type 2 diabetes is usually made clinically. While either type of diabetes can occur at any age, type 1 diabetes usually affects younger people (children, adolescents, and young adults), and type 2 diabetes occurs in those over the age of 40 years. Details of diagnostic criteria for diabetes are shown in Fig. 1.

Individuals who develop type 2 diabetes are more likely to have a family history of the disease and are commonly obese or overweight. Further, the

Fig. 1. Diabetes Diagnostic Criteria.

finding of a skin condition called acanthosis nigricans (thickening and darkening of the skin at the nape of the neck or in flexural creases) is a sign of underlying insulin resistance associated with type 2 diabetes. Measurement of the islet cell antigen antibodies and/or insulin antibodies may help distinguish type 1 from type 2 diabetes. This test is particularly useful in those individuals who have latent autoimmune diabetes of adults and who present as if they have type 2 diabetes. These individuals are usually not obese and do not have a strong family history of type 2 diabetes. Measurement of circulating insulin or C-peptide concentrations does not always help distinguish type 1 from type 2 diabetes *(14)*.

In women who are pregnant, screening for gestational diabetes is done by performing a 50-g glucose challenge test *(10)*. If the glucose is greater than or equal to 140 mg/dl 1 h after the administration of the glucose (which need not be done in the fasting state), the subject then undergoes a 3 h 100-g oral glucose tolerance test. Gestational diabetes is confirmed if there are two abnormal values out of four measured (fasting, 1-h, 2-h, and 3-h) values in this 3-h oral glucose tolerance test (abnormal values are greater than or equal to 105 mg/dl for fasting, greater than or equal to 190 mg/dl at 1 h, greater than or equal to 165 mg/dl at 2 h, and greater than or equal to 145 mg/dl at 3 h) *(15)*. Gestational diabetes usually develops toward the end of the second trimester or beginning of the third trimester and may be an indicator of predisposition for development or continuation of diabetes or the development of diabetes postpartum *(15)*. Hence, screening for this condition is usually performed between the 24th and 28th week of pregnancy, but should be done earlier in women with a previous history of gestational diabetes or those who are at greater risk for the development of this condition *(10)*.

TREATMENT

There are many pharmacologic agents available for the treatment of insulin resistance as well as the insulin deficiency in type 2 diabetes. These medications are discussed in greater detail in other chapters. In brief, the drugs used to treat insulin resistance include the biguanide metformin and the thiazolidinediones (TZDs) rosiglitazone and pioglitazone. Drugs that enhance insulin secretion include sulfonylureas, non-sulfonylurea agents that act like sulfonylureas, glucagon-like-peptide analogues, and DPP-IV inhibitors. Medications are also available that delay the absorption of glucose from the gastrointestinal tract (α-glucosidase inhibitors), and of course, insulin itself. Finally, an analogue of amylin, a peptide which is cosecreted from the β cell with insulin, is available to be used in conjunction with insulin in both type 1 and type 2 diabetes; this medication is called pramlintide (symlin) *(7)*.

Treatment of adults with hyperglycemia is detailed in an American Diabetes Association (ADA) and European Association for the Study of Diabetes (EADS) consensus statement. It details the following as primary treatment strategy: (1) intervention at diagnosis with lifestyle changes (medical nutrition therapy and exercise) and the oral agent metformin and (2) the addition of other oral agents (and, if needed, early insulin therapy) to achieve target goals. The general benchmark for gauging success of diabetes management is the hemoglobin A1c (henceforth referred to as simply "A1c" and commonly referred to as A1c or "HbA1c") test, which has a value of 6% or less in the non-diabetic population. The ADA-EASD method is to be used as the primary system to lower diabetes patients' A1c to target, which is below 7% for most patients, provided this can be achieved safely *(16)*. Achieving and maintaining glucose as close to the non-diabetic range as possible, and changing interventions at as rapid a pace as possible for safe titration, is most beneficial for patients' health in this scheme *(16)*. Treatment must be individualized with targets for glucose control based on other factors, including risk of additional complications with treatment, age of the patient, ability to comply with the treatment regimen and projected longevity of the individual, and presence or absence of chronic complications of the disease *(7)*.

The ADA-EASD algorithm took the evidence for this method of lowering A1c into account as well as its expense to the patient. Of note, this statement was developed well *before* publications and black box warnings that raised concerns about increased risk of myocardial infarction with use of rosiglitazone and congestive heart failure with both rosiglitazone and pioglitazone. Greater caution in using the thiazolidinediones may be warranted now according to individual patients' concerns. The following medications were not included in the consensus due to lack of glucose-lowering effectiveness, limited clinical data, and/or relative expense: pramlintide, exenatide, α-glucosidase inhibitors, the glinides, and DPP-IV inhibitors. Despite their exclusion in the algorithm, these are appropriate choices in individual patients to achieve glycemic and weight loss goals. Individuals presenting with weight loss and/or severe hyperglycemic symptoms require immediate initiation of insulin at time of diagnosis *(7)*.

Treatment of type 2 diabetes usually requires initiation with one or sometimes two medications together with lifestyle modification and the addition of more medications with time to achieve and maintain target goals. Because of the disease's natural history, use of insulin is ultimately required in many patients. In these patients, insulin may be initiated with just one injection of basal insulin at night, but often this is inadequate to achieve ideal glucose control; patients then require more frequent injections of insulin, ranging from twice daily to multiple daily injections (basal–prandial insulin treatment) *(7)*.

In type 1 diabetes, insulin therapy involves multiple daily insulin injections that are tailored to the individual's needs. Several studies have shown that intensive treatment with insulin in type 1 or 2 diabetes, or oral medications in type 2 diabetes, is associated with a significant reduction in risk for the development or progression of the early microvascular complications of the disease *(12,17,18)*. The United Kingdom Prospective Diabetes Study (UKPDS), a 4585-patient observational study, showed that a 1% reduction in A1c was associated with a 37% mean risk reduction for the development or progression of microvascular complications and a 14% mean reduction in risk for myocardial infarction in patients with type 2 diabetes *(12)*.

Similarly, the Kumamoto Study showed that good glycemic control achieved using insulin treatment delayed the onset and progression of diabetic retinopathy, nephropathy, and neuropathies in Japanese patients with type 2 diabetes *(18)*. A cost–effect analysis using a computer simulation to estimate lifetime benefits and costs of insulin therapy in a sample of 120,000 people with type 2 diabetes indicated great improvement in quality and longevity of life, far outweighing the disadvantages of treatment *(4)*. All studies confirm that early intensive insulin treatment in both type 1 and type 2 diabetes benefits health and quality of life for patients and is cost effective in the long term.

The benefits of intensive insulin therapy with frequent injections of insulin do come at a price, however. Insulin therapy carries the associated risk of a dangerously low level of blood glucose (hypoglycemia) in a small number of patients when the insulin dose is overmatched with the amount of food ingested. Hypoglycemia can cause dizziness and nausea and, in severe cases only, coma or death. As a result, it is the primary impediment to insulin therapy and prevents many patients from the benefits which treatment so clearly brings *(7)*.

DEPRESSION AND DIABETES

Because diabetes is a chronic disease, the burden of treatment takes a serious toll on most patients, including managing complications and the fears associated with them and dealing with weight gain and the associated social stigma. It is now common for people with any type of diabetes to be affected by major clinical depression: studies have found that up to 30% of patients with diabetes have comorbid depression *(18–20)*. If the patients' quality of life and overall health are to be a priority in diabetes treatment, this observation cannot be ignored. Studies have shown that patients with diabetes and depression have poor adherence to oral diabetes agents and other medications, have more sedentary lifestyles, and do not eat healthily when compared with non-depressed patients with diabetes *(19,21)*. Diabetes complicated by depression is also associated with higher A1c levels and obesity (defined as having a body mass index greater than $30 \, \text{kg/m}^2$) when compared with people with diabetes who are not

depressed *(20)*. These associations become large obstacles when insulin therapy is implemented or intensified in patients with both diabetes and depression, especially when depression is undiagnosed, which it commonly is.

Depression is thought to be associated with insulin resistance (independent of weight) and can be improved by antidepressive treatment *(22,23)*. However, because many antidepressants *cause* weight gain and diabetes, extra caution is warranted *(24)*.

FEAR OF HYPOGLYCEMIA AND ASSOCIATED WEIGHT GAIN

As mentioned previously, one common consequence of insulin treatment is the risk of hypoglycemia. However, the perceived threat of a hypoglycemic episode has been shown to greatly exceed the actual incidence of an event in patients with diabetes *(4)*. Therefore, individuals may increase caloric intake to proactively avoid such an event, which may result in weight gain. It was demonstrated in the Diabetes Control and Complications Trial (DCCT) that patients who had experienced one or more episodes of hypoglycemia gained 6.8 kg, significantly more than patients with no severe hypoglycemia (2.2 kg) *(4)*.

Two novel agents based on glucoregulatory hormones have recently become available and may be appropriate in managing weight in patients with diabetes. The amylin agonist pramlintide (Symlin®) and the incretin mimetic exenatide (Byetta®) have both demonstrated potential in improving glycemic control in patients with diabetes along with the added benefit of weight loss when compared with placebo *(25,26)*. Pramlintide is approved for use in individuals taking insulin (both type 1 and type 2 diabetes). Exenatide is approved for use in combination with metformin, sulfonylureas, and/or TZDs in subjects with type 2 diabetes.

LIFESTYLE CHANGES

The American Diabetes Association recommends that overweight patients with diabetes should lose 5%–7% of their initial weight, irrespective of its value *(27)*. For overweight people with diabetes, weight loss improves insulin sensitivity and glycemic control *(27)*, and even moderate intentional weight loss may be associated with reduced mortality *(28)*. Weight loss also improves lipid profiles and blood pressure *(29)* as well as mental health and overall quality of life *(30,31)*. These benefits, while significant, are clinically meaningful only if weight loss is sustained over time *(32)*.

Weight loss diets with low levels of carbohydrate and high levels of protein are gaining in popularity. A recent small study (n = 12) over 5 weeks compared

a high-protein diet (40% carbohydrate, 30% protein, and 30% fat) to a high-carbohydrate diet (55% carbohydrate, 15% protein, and 30% fat) in patients with type 2 diabetes. Patients in both groups lost weight (-2.2 and -2.5 kg, respectively). However, mean A1c and post prandial plasma glucose decreased significantly ($p < 0.05$) only in the patients with type 2 diabetes on high-protein diet *(33)*.

Regular exercise promotes long-term weight loss, provided that the regimen is habitual and consistent *(34)*. Exercise can lower blood glucose, improve the body's ability to use glucose, and decrease the amount of insulin needed *(35)*. However, as those with type 2 diabetes generally have a lower level of fitness than non-diabetic individuals, exercise intensity should be at a comfortable level in the initial periods of training and should progress cautiously as tolerance for activity improves *(36)*.

Lifestyle changes such as those outlined above can be discussed with patients in group therapy sessions. Regular meetings with patients, possibly involving psychologists and dietitians, can help reinforce and encourage patients to continue with their diet and exercise programs *(37)*. Psychologists can help in this setting by introducing behavioral therapy aimed at improving a patient's body image and attitude to eating *(32)*.

IMPORTANCE OF SELF-MANAGEMENT

Self-management is an essential element of health in people with type 1 and type 2 diabetes. Nurses and dieticians regularly address barriers to successful self-care by identifying specific areas of self-management for improvement and setting realistic goals with the patient regarding food, medications, and insulin. A comprehensive assessment of the barriers to self-care can recognize precise areas with which the patient may need encouragement and help. Awareness of these barriers can be used to tailor the educational material received from nurses and dietitians, incorporating information and learning about these barriers can support the patient's diabetes control and care.

These ongoing, tailored self-management interventions should be integrated into routine care as they prove useful in the continuing education of the patient. The complementary nature of self-management education to diabetes clinical goals as set by the entire patient care team (including the patient, their physician, a nurse practitioner, a nurse educator, a dietitian, and, if possible, an exercise physiologist) is very constructive and can have results of surprisingly great impact; these results tend to strengthen as the relationship between the patient and the team strengthens. For example, as little as a brief self-management program aimed at helping patients to adopt low-fat eating patterns and increase physical activity levels via motivational interviews and follow-up phone contact with their patient care team has reported good success in weight

maintenance *(38)*. A similar study focused on improving self-care behavior in diabetes has reported both weight loss and improvements in both healthy eating and glycemic control *(39)*.

CONCLUSION

As the incidence of diabetes grows worldwide, the importance of diabetes self-management education cannot be underestimated by any member of the patient care team. The lasting impact of the patient–team interactions is commonly reflected in the patient's commitment and success in managing their diabetes and quality of life. A sense of community and support is often the key to empowering patients to take control of their diabetes, and the patient care team must be strong enough to uphold that responsibility using good communication and quality care.

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