Diagnosis, Classification, and Lifestyle Treatment of Diabetes

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Editor's note: This article is the second in an eight-part series reviewing the fundamentals of diabetes care for physicians in training. This series is an updated adaptation of a 12-part series published in Clinical Diabetes between 2006 and 2009. The previous series, and earlier installments of this one, can be found online at the journal Web site (http://clinical.diabetesjournals.org).

During internship and residency, young physicians encounter a myriad of diseases and symptoms in the course of training. As discussed in the previous installment of this series (Clinical Diabetes 27:160–163, 2009), diabetes is a major issue in U.S. health care and is growing rapidly. Medical professionals can expect to spend a large portion of their time caring for diabetic patients in inpatient and outpatient settings as the prevalence of this disease increases steadily.

Central to the treatment of patients with diabetes is the understanding of the disease itself. Previously, physicians classified diabetes based on the treatment required to control the disorder (insulin-dependent versus non–insulin-dependent diabetes) or age at which the disorder develops (juvenile diabetes or late-onset autoimmune diabetes of adulthood). As our understanding of diabetes has deepened, the diagnostic criteria and classification scheme of diabetes has changed as well.

Different therapies now target the underlying mechanisms of diabetes, such as insulin deficiency, insulin resistance, and other aspects of the disease process. To improve the health care of people with diabetes, the American Diabetes Association (ADA) no longer recommends classification of diabetes based on treatment of hyperglycemia, but rather on the underlying mechanism involved.1,2 The underlying mechanisms of diabetes were discussed in detail in our previous installment. This issue will focus on the classification scheme for diabetes, which is important for several reasons.

In addition to offering expedient and up-to-date health care for patients, there are other important reasons to have a thorough understanding of the classification of diabetes. A diagnosis of diabetes can have a major effect on the cost of an individual’s health insurance premiums. In many situations, patients with diabetes may even be considered uninsurable, which limits their ability to become self-employed or to obtain insurance for their family. There are also important ramifications in other areas such as insulin use. For example, people who use insulin and are commercial drivers must apply for a waiver in order to legally operate a commercial vehicle across state lines.3 It is important, therefore, to avoid inappropriate diagnoses.

ADA revised its criteria for the diagnosis of diabetes in 1997.4 This classification provides for diagnosis of diabetes based on fasting or postprandial glucose level. These criteria specify that individuals have diabetes if they 1) have symptoms of diabetes such as polyuria, polydipsia, or unexplained weight loss and a random plasma glucose measurement > 200 mg/dl or 2) have a fasting plasma glucose ≥ 126 mg/dl or a 2-hour plasma glucose level ≥ 200 mg/dl after consumption of 75 g of glucose. It is important to note that glucose readings and A1C should be performed in a laboratory setting rather than with a handheld glucose meter or point-of-care measurement device because of the potential for error with such devices. It is also advisable to repeat glucose testing on a different day. Additionally, the glucose tolerance test is not recommended for routine diagnosis of diabetes because of the higher degree of reproducibility of the fasting glucose test.

Beginning this year, ADA also recognizes a diagnosis of diabetes based on elevated A1C level. Because A1C results represent an integrated measurement of hyperglycemia during a 2- to 3-month period and are more reproducible than plasma glucose readings, A1C levels ≥ 6.5% are now considered diagnostic of diabetes.

It is also important to consider that disorders that affect glycosylation of hemoglobin (such as hemoglobinopathies, including sickle cell trait and disease) and red blood cell turnover (such as iron-deficient anemia) invalidate A1C...
United States. Although this form of diabetes constitutes ~10% of diabetes in the United States. It is caused by an absolute deficiency in insulin production. It is thought to arise from autoimmune destruction of the β-cells of the pancreas in genetically susceptible individuals, and constitutes ~10% of diabetes in the United States. Although this form of diabetes is more common in childhood, it can occur at any time in life.

Adults misdiagnosed as having type 2 rather than type 1 diabetes may be expected to have very limited or transient response to oral agents and to progress rapidly to insulin therapy. Because these patients eventually develop an absolute deficiency of insulin, insulin is the mainstay of treatment, although adjunctive therapies such as pramlintide are now available. Progression to absolute insulin deficiency is variable and tends to be rapid in children and slower in adults.

There are several markers of autoimmunity available to help identify people with type 1 diabetes; these include anti-islet, anti-glutamic acid decarboxylase-65 antibodies (anti-GAD), anti tyrosine phosphatase (anti IA2), and anti-insulin autoantibodies. Type 1 diabetes is further sub-classified into type 1A diabetes if autoimmune markers are positive and type 1B diabetes if such markers are not present.

Approximately 90% of newly presenting patients will have at least one positive antibody titer. Positivity varies based on age, duration of diabetes, and ethnicity. Anti-GAD antibodies are positive in 70–80% of patients at the time of diagnosis. They are also more commonly positive in adults who develop type 1 diabetes and generally remain positive, whereas anti-insulin antibodies are not reliably measured after initiation of insulin therapy. Other patients clearly have complete or near-complete insulin deficiency and other autoimmune diseases such as autoimmune hypothyroidism, yet remain antibody-negative. These patients are considered to have type 1B diabetes.

It is important to note that history of diabetic ketoacidosis (DKA) is suggestive but not diagnostic of type 1 diabetes because many patients with type 2 diabetes may also develop this complication. Type 1 diabetes may also present during pregnancy.1,2 There is also evidence that early and intensive use of insulin in adults presenting with type 1 diabetes increases their ability to produce insulin endogenously, which further underscores the importance of early and accurate diagnosis of type 1 diabetes.3

Type 2 Diabetes
Type 2 diabetes is a heterogeneous group of conditions that constitute ~90% of all diabetes cases in the United States. Previously, type 2 diabetes was known as non–insulin-dependent diabetes or adult-onset diabetes. As described in our previous installment, it involves insulin resistance and relative insulin deficiency rather than the absolute insulin deficiency seen in type 1 diabetes.

Insulin resistance is thought to precede insulin deficiency in most patients, and autoimmune destruction of β-cells does not occur, although β-cell mass may be reduced. Because the insulin deficiency is relative rather than absolute, DKA occurs less frequently in type 2 diabetes than in type 1 diabetes.

Therapy for type 2 diabetes varies considerably from that for type 1 diabetes. The majority of patients with this form of diabetes are clinically obese, and exercise and weight loss lead to improvements in the disease state and even clinical remission in some individuals. Pharmacotherapies directed toward increasing insulin sensitivity and increasing β-cell insulin production are useful in type 2 but not in type 1 diabetes. Unlike in type 1 diabetes, there is a strong genetic predisposition to developing type 2 diabetes, and the presence of several family members with type 2 diabetes suggests the diagnosis.
Gestational Diabetes Mellitus

Gestational diabetes mellitus (GDM) is defined as “any degree of glucose intolerance with onset or first recognition during pregnancy.” Unlike other forms of diabetes, GDM utilizes a different set of diagnostic criteria and screening because normal physiological levels of glucose are different during pregnancy.

It is important to note that GDM is a powerful predictor of type 2 diabetes later in life. Some studies have demonstrated that as many as 70% of women who experience GDM will develop type 2 diabetes within 10 years after delivery. History of GDM, therefore, is an indicator of the presence of type 2, rather than type 1, diabetes in a hyperglycemic woman.

Other Specific Types of Diabetes

ADA recognizes more than 56 other specific types of diabetes. Some of these are quite rare, whereas others are much more common. Understanding of these different forms of diabetes is important because their treatment modalities sometimes differ significantly from other forms of diabetes.

Several other forms of diabetes are associated with insulin deficiency related to nonimmune-mediated injury to the β-cells or to the pancreas as a whole. This group of disorders includes such diseases as cystic fibrosis, acute or chronic pancreatitis, trauma, partial or complete pancreatic resection (Whipple procedure), hemochromatosis, and other causes.

The degree of diabetes is generally proportional to the amount of injury to the pancreatic β-cell mass, which is disproportionately located in the head of the pancreas. Certain individuals may have limited β-cell reserve (such as those with early type 2 diabetes) before pancreatic injury and therefore develop diabetes after what appears to be a minor loss of pancreatic tissue. Another clinically important aspect in caring for these patients is that they may be more susceptible to hypoglycemia if they have lost α-cells in addition to β-cells and therefore do not have normal glucagon secretion.

Several hormones oppose the action of insulin and are therefore diabetogenic if secreted in excess. Examples include cortisol (Cushing’s syndrome), growth hormone (acromegaly), glucagon (pancreatic glucagonoma), and epinephrine (pheochromocytoma). Many of these hormones lead to hyperglycemia by increasing hepatic glucose production or decreasing insulin sensitivity. Conditions that cause excess secretion of these substances can result in glucose intolerance, elevated fasting glucose levels, or frank diabetes.

It is important to note unusual physical stigmata of these diseases when evaluating patients for diabetes, especially if they are newly presenting, exhibit more rapid progression, or are resistant to therapy. Some estimates suggest that up to 3% of patients with poorly controlled glucose in diabetes clinics may have Cushing’s syndrome.

Several monogenetic defects in β-cell function have been described. They are collectively referred to as maturity-onset diabetes of the young (MODY). Typically, they manifest themselves in infancy or childhood, and cause impaired insulin secretion with relatively normal insulin action. They are inherited in an autosomal-dominant manner.

There are also several genetic disorders that lead to abnormal insulin action. Examples include Leprechaunism, type A insulin resistance, and Rabson-Mendenhall syndrome.

Medical treatments of diabetes are becoming increasingly focused on specific forms of diabetes and on aspects of the diabetic state, such as insulin resistance, insulin deficiency, and increased hepatic glucose output. It is increasingly important to accurately diagnose patients with the correct form of diabetes to control glucose levels and prevent complications. In the case of type 1 diabetes, early diagnosis and treatment can lead to prolonged ability to produce insulin endogenously and can lower the risk of microvascular complications. Similarly, early recognition of impaired fasting glucose may delay or avert the development of type 2 diabetes, especially through aggressive diet modification and exercise with resultant weight loss.

Diet and Exercise

Lifestyle therapies are the cornerstone of diabetes treatment. An unhealthy lifestyle featuring a lack of physical activity and excessive eating initiates and propagates the majority of type 2 diabetes.

As discussed in our previous installment, the incidence and prevalence of obesity is rising quickly in the United States and throughout the world. The frequency of diabetes has risen in tandem with overweight and obesity in essentially all age-groups and ethnicities in the United States, and not by coincidence. Studies have thoroughly demonstrated strong relationships between excess weight and the risk of developing type 2 diabetes, hypertension, and hyperlipidemia.

Physicians are frequently challenged with the task of motivating patients to lose weight and exercise to improve their diabetes control and therefore slow or even attempt to reverse the natural course of the disease.

Lifestyle modification is an equally integral part of type 1 diabetes management. Patients with type 1 diabetes, because of a universal need for insulin, must learn to count or
at least closely estimate the amount of carbohydrate they consume to help regulate their blood glucose levels and adjust their insulin doses. Failure to do so can lead to dangerous hyperglycemia or hypoglycemia.

Primary Prevention of Diabetes

It is difficult to overstate the importance of the relationship between lifestyle and the risk of developing type 2 diabetes. One recent study demonstrated that both women and men with BMIs > 35 kg/m² had a 20 times higher risk of developing diabetes compared to people with a BMI of 18.5–24.9 kg/m². Furthermore, prospective studies have demonstrated that lifestyle modification in the form of diet and regular moderate exercise sharply decreases the likelihood of developing type 2 diabetes in high-risk individuals with impaired glucose tolerance or impaired fasting glucose. The effectiveness of this intervention supersedes that of metformin therapy. It is crucial, therefore, to properly educate obese patients, patients with glucose intolerance, and those with impaired fasting glucose about the significance of exercise and weight loss in preventing diabetes. Many patients may assume that medical therapy is the more important approach.

Control of Existing Diabetes

Lifestyle interventions are not only beneficial before the development of diabetes. Several studies have clearly demonstrated the benefits of control over diet, exercise, and weight loss in individuals already diagnosed with diabetes. Dietary restriction to 1,100 kcal/day has been shown to decrease fasting blood glucose levels in obese patients with diabetes and even those without diabetes in as few as 4 days. This improvement is likely the result of decreased hepatic glucose output. After 28 days of calorie restriction, there is further decline in fasting glucose levels of obese diabetic subjects, and insulin sensitivity is significantly improved. It is also noteworthy that improvement in insulin sensitivity correlates well with decrease in fasting glucose and with degree of insulin sensitivity. These changes occurred with an average weight loss of only 6 kg. These interventions have not been shown to improve insulin secretory capacity.

Obese people also have a high incidence of hypertension and hyperlipidemia compared to nonobese people; this may further increase their risk of microvascular and macrovascular complications of diabetes. Weight loss has been shown to decrease systolic and diastolic blood pressure, as well as LDL cholesterol and lipid levels in obese diabetic patients. Ongoing trials are exploring the potential ability of intensive lifestyle interventions to decrease the rate of cardiovascular disease events in type 2 diabetes.

Dietary Considerations

Carbohydrate

People with type 1 diabetes, because they experience absolute insulin deficiency, must use insulin to control glucose excursions after meals. Since 1994, ADA has recommended that patients with type 1 diabetes consume 60–70% of their total calories from carbohydrate and monounsaturated fat. Although some studies have considered whether a preponderance of calories from unsaturated fat or carbohydrate may be more beneficial, none has demonstrated a clear benefit.

There are demonstrated improvements, however, in adjusting short-acting insulin doses based on the carbohydrate content of food for patients using a basal-bolus insulin or continuous subcutaneous insulin infusion regimen. Similarly, patients on fixed doses of short-acting insulin should attempt to keep the amount of carbohydrate they consume relatively constant from meal to meal. Recommendations for carbohydrate consumption in people with type 2 diabetes are similar to recommendations for those with type 1 diabetes. About 60–70% of total calories should come from carbohydrate or monounsaturated fat. However, there is some concern that increased unsaturated fat consumption may promote weight gain in obese patients with type 2 diabetes and thereby decrease insulin sensitivity. Glycemic excursions appear to be similar between starches and sucrose (“table sugar”) and, therefore, sucrose does not need to be eliminated from the diet.

The “glycemic index” attempts to compare the glycemic effects of various foods to a standard, such as white bread. Although several authors have proposed its clinical usefulness in controlling postprandial hyperglycemia, several prospective studies have not demonstrated a clear improvement in A1C in patients using low-glycemic index diets. One cross-sectional study suggested a relationship in low-glycemic index diets and low A1C levels in patients with type 1 diabetes, but it is important to note that this study did not control for patients using once-daily, twice-daily, or intensive insulin therapy regimens to control their glucose excursions. Another more recent meta-analysis of low-glycemic index diets did suggest a mild but significant improvement in A1C. There may exist, therefore, a small benefit in pursuing a low-glycemic index diet for patients with diabetes. This benefit, however, appears to be less than the benefit that can be derived from counting or controlling the total amount of carbohydrate consumed at meals.

Many sweeteners are available to the general public. Perhaps the most
common is sucrose. Studies comparing the effects of equal amounts of sucrose and starch on glycemic control have virtually no differences. As described above, sucrose should be adequately covered by short-acting insulin at mealtime but does not need to be eliminated from the diet. Fructose may cause less postprandial hyperglycemia, but there is some evidence suggesting that it may also lead to or worsen hyperlipidemia. Therefore, adding fructose to the diet as a sweetening agent is not recommended by ADA, although naturally occurring fructose in foods such as fruits does not need to be avoided.

The U.S. Food and Drug Administration (FDA) has approved several sugar alcohols for use as sweeteners. These include products such as sorbitol, a common sweetener in chewing gum. Sugar alcohols cause less hyperglycemia than naturally occurring sugars and may also decrease the risk of dental carries. They are only partially absorbed from the intestinal tract and therefore may lead to diarrhea or gastrointestinal discomfort, especially if consumed in higher amounts. They provide approximately half the calories of natural sugars and should be included in carbohydrate counting at half the impact of sucrose. These products have not been shown to facilitate weight loss or improve glycemic control.

Several sweeteners that are non-nutritive and do not affect blood glucose levels are also available to the public. These include aspartame, sucralose, saccharin, neotame, and acesulfame potassium. Although at one time linked to carcinogenesis in laboratory animals at extremely high doses, saccharin is no longer considered a cancer-causing chemical by the FDA. One of the most recently released sweeteners, sucralose, has been shown to have no significant effect on blood glucose levels and therefore may be omitted from carbohydrate calculations. Use of these sweeteners has not been shown to facilitate weight loss or improve glycemic control.

Patients should exercise caution whenever introducing artificial sweeteners into the diet or when decreasing their carbohydrate consumption. Making these changes without adjustment in diabetes medications could cause hypoglycemia, especially in patients using insulin or insulin secretagogues.

**Protein**

Although the majority of clinical focus in the management of patients with diabetes is on carbohydrate metabolism, protein metabolism in the state of diabetes is also abnormal. Patients with type 2 diabetes exhibit a more negative nitrogen balance than normal subjects. Protein degradation appears to be exacerbated by hyperglycemia and improved by controlling glucose levels with insulin therapy.

These studies suggest that protein requirements for people with type 2 diabetes may be slightly greater than those for nondiabetic individuals. However, as pointed out by Franz et al., most individuals in the United States consume considerably more protein that the recommended daily allowance.

Patients with type 1 diabetes can and do convert amino acids into glucose depending on level of insulinization; therefore, protein consumption may cause hyperglycemia. Studies of patients with type 2 diabetes have demonstrated that protein consumption does not increase plasma glucose concentrations and that endogenous insulin release is stimulated by protein consumption.

There may be an association between high-protein diets and the risk of developing diabetic nephropathy. In a cross-sectional study of patients with type 1 diabetes, patients with microalbuminuria were more likely than patients with microalbuminuria or normal albumin excretion to report consuming >20% of their calories in the form of protein. High-protein diets, therefore, are currently not advisable.

**Dietary fat**

Recommendations regarding fat in the diet of people with diabetes are similar to recommendations for patients with coronary artery disease. This is primarily because of studies that show that the risk of myocardial infarction in diabetic patients is similar to the risk of nondiabetic patients who have already suffered a myocardial infarction. Because saturated fats are the major dietary determinants of serum LDL cholesterol levels, people with diabetes should strive to keep them to <7% of total daily calories and to minimize consumption of trans fatty acids. Cholesterol consumption should be <200 mg/day.

When incorporated into a controlled-calorie diet in which no weight loss is occurring, programs that emphasize either carbohydrate or monounsaturated fats both lower cholesterol, but the higher-carbohydrate diets may exacerbate hyperglycemia. In diets in which total calories were reduced to facilitate weight loss, however, the hyperglycemic effect of the high-carbohydrate diet appeared mitigated.

Mediterranean-style diets that are high in polyunsaturated fats have been associated with lower mortality in elderly Europeans, but this study was not specific for people with diabetes. Diets high in fish oil may decrease the risk of cardiovascular disease and all-cause mortality.

Plant sterols are plant esters that decrease intestinal absorption of both dietary and hepatobiliary...
cholesterol. They have been shown in prospective studies of diabetic patients to decrease LDL cholesterol. ADA recommends that if they are used in the diet to decrease cholesterol, they should replace cholesterol rather than simply be added to the diet to avoid unnecessary weight gain.24,36

There has been a great deal of interest in using micronutrients such as chromium and zinc, antioxidants, and herbal supplements to improve diabetes control. Although some small studies have suggested a benefit from chromium, other studies and meta-analyses have not reached the same conclusion. Currently, there are no large, convincing studies that prove the benefit of specific micronutrients in the management of diabetes.24

Considerable attention and marketing has been focused on the macronutrient content of diets. A recent study suggested that a low-carbohydrate, high-fat, and high-protein diet may yield greater weight loss than other diets in nondiabetic patients.37 Similar diets studied in diabetic patients have also suggested that a low-carbohydrate diet may produce similar or superior weight loss than balanced diets. Changes in triglycerides may be more favorable in low-carbohydrate diets, and A1C levels may be lower.38,39 Meta-analysis of several studies, however, suggested that low-carbohydrate diets may raise LDL cholesterol levels.38,40

It is important to note that the existing studies of low-carbohydrate diets are short-term studies; the long-term effects of such diets are unknown. This is especially concerning because of their widespread use and the association of diabetic kidney disease with diets consisting of >20% of calories from protein. For these reasons, a low-carbohydrate diet (<130 g of total carbohydrate per day) is not recommended by ADA.24

**Exercise Considerations**

Patients with type 1 or type 2 diabetes have an increase risk of coronary artery disease. ADA recommends that patients who plan to begin a moderate- to high-intensity exercise program undergo screening for cardiovascular disease if they are >35 years of age or if they are >25 years of age and have had type 2 diabetes for >10 years or type 1 diabetes for >15 years, have an additional risk factor for coronary disease, or have microvascular disease, peripheral vascular disease, or autonomic neuropathy. Decisions regarding screening of patients who plan low levels of physical activity, such as walking, are left to the discretion of their treating physicians. Because some activities can lead to retinal hemorrhage or detached retina in the setting of proliferative retinopathy, patients with this condition should consult their ophthalmologist before beginning an exercise regimen.41

People with type 1 diabetes who begin an exercise regimen should tailor their exercise to their specific condition. For example, patients with peripheral neuropathy must take precautions to avoid blisters and abrasions and check closely for such conditions after exercise. Patients should consider delaying exercise if their blood glucose level is >250 mg/dl and ketones are present or if their glucose level is >300 mg/dl. They should monitor their blood glucose before and after physical activity and be cautious about hypoglycemia, which can develop during or even several hours after exercise. They should have carbohydrate available and consume it as necessary to avoid hypoglycemia. Although studies have not demonstrated a clear benefit of aerobic exercise on A1C levels in type 1 diabetes, it is clearly beneficial in controlling other risk factors for cardiovascular disease.41

Physical exercise is a key component of lifestyle modification that can help individuals prevent or control type 2 diabetes. Although diet is probably more important in the initial phases of weight loss, incorporating exercise as part of a weight-loss regimen helps maintain weight loss and prevent regaining of weight.42 Mild to moderate activity levels have been associated with a lower risk of developing diabetes or pre-diabetes. Men with low degrees of cardiorespiratory fitness may possess up to a 1.9-fold increased risk of developing impaired fasting glucose compared to men with high degrees of fitness.43

Patients should understand that the amount of exercise that produces a beneficial effect on health is not large; as little as 30 minutes of moderate physical activity daily may offer protection from diabetes.42,44 As with the lowering of A1C levels, there is a gradient of benefit with higher levels of exercise and activity. Greater levels of physical activity are associated with lower risks of developing diabetes in women compared to lesser levels of activity.45 These studies indicate that exercise should be a mainstay of primary prevention of diabetes.

In patients with type 2 diabetes, structured regimens of physical activity for 8 weeks or longer improved A1C independent of changes in body mass. There may also be further improvement in A1C with increasing intensity of exercise.46,47

Exercise in type 2 diabetes has not been associated with peripheral neuropathy or worsening of nonproliferative retinopathy. Physical activity may cause transient increases in urinary albumin excretion, but exercise has not been shown.
to increase the rate of progression of diabetic kidney disease. Resistance exercise may be incorporated into a weekly exercise regimen in the absence of contraindications.46

As further evidence regarding the benefit of exercise, in men with diabetes, the degree of physical fitness correlated with overall mortality, and this association was independent of BMI.42,48

When confronted with newly presenting patients with diabetes, glucose intolerance, or impaired fasting glucose, one of the most vexing questions physicians face posed is to what extent patients should rely on exercise, weight loss, and dietary modification to control the disease. Evidence supports the inclusion of dietary and lifestyle modification as a mainstay of therapy to control diabetes.

With many oral and injectable pharmaceutical agents available to help patients control their glucose levels, it is easy for practitioners to overlook or forget to emphasize and reinforce the importance of lifestyle modification. Despite being one of the most time-consuming topics to discuss with patients, it is probably the most important discussion for patients to have with their physicians in regard to diabetes control and prevention of disease progression and complications.

REFERENCES


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