

Diabetes mellitus and periodontal disease

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Definition

Diabetes mellitus is a clinically and genetically heterogeneous group of metabolic disorders manifested by abnormally high levels of glucose in the blood. The hyperglycemia is the result of a deficiency of insulin secretion caused by pancreatic β -cell dysfunction or of resistance to the action of insulin in liver and muscle, or a combination of these. Frequently this metabolic disarrangement is associated with alterations in adipocyte metabolism. Diabetes is a syndrome and it is now recognized that chronic hyperglycemia leads to long-term damage to different organs including the heart, eyes, kidneys, nerves, and vascular system.

There are several etiologies for diabetes and although establishing the type of diabetes for each patient is important, understanding the pathophysiology of the various forms of the disease is the key to appropriate treatment. The current classification of diabetes is based upon the pathophysiology of each form of the disease.

Physiological action of insulin

Plasma glucose is regulated over a relatively narrow range (55–165 mg/dl) during the course of 24 h, despite wide fluctuations in glucose supply and consumption. Insulin is the primary regulator of glucose homeostasis but it also plays a critical role in fat and protein metabolism. Insulin production and secretion increase with food ingestion and fall with food deprivation. The hormone has major effects on muscle, adipose tissue, and the liver. Insulin allows glucose from the bloodstream to enter the target tissues where glucose is used for energy.

The insulin receptor is a heterotetrameric protein consisting of two extracellular α -subunits and two transmembrane β -subunits. The binding of the ligand to the α -subunit of the insulin receptor stimulates the

tyrosine kinase activity intrinsic to the β -subunit of the receptor. Extensive studies have indicated that the ability of the receptor to autophosphorylate and to phosphorylate intracellular substrates is essential for its mediation of the complex cellular responses to insulin (42).

Insulin is secreted by the β cell of the pancreas directly into the portal circulation. Insulin suppresses hepatic glucose output by stimulating glycogen synthesis and inhibiting glycogenolysis and gluconeogenesis, thus decreasing the flow of gluconeogenic precursors and free fatty acids to the liver. In type 2 diabetes, increased rates of hepatic glucose production result in the development of overt hyperglycemia, especially fasting hyperglycemia (31).

Under basal conditions approximately 50% of all glucose utilization occurs in the brain, which is insulin independent. Another 25% of glucose uptake occurs in the splanchnic area (liver and gastrointestinal tissues) and is also insulin independent (30). The remaining 25% of glucose metabolism in the post-absorptive state takes place in insulin-dependent tissues, primarily muscle (29). Approximately 85% of endogenous glucose production is derived from the liver, and the remainder is produced by the kidney. About half of basal hepatic glucose production is derived from glycogenolysis and half from gluconeogenesis (41, 95). Insulin is an anabolic hormone that promotes lipid synthesis and suppresses lipid degradation. In addition to promoting lipogenesis in the liver, insulin also stimulates lipid synthesis enzymes (fatty acid synthase, acetyl-coenzyme A carboxylase) and inhibits lipolysis in adipose tissue. The anti-lipolysis effect of insulin is primarily mediated by inhibition of hormone-sensitive lipase.

Glucagon is a hormone secreted by the α cells of the pancreas. Glucagon is also important in the maintenance of normal glucose homeostasis. During post-absorptive conditions approximately half of the total hepatic glucose output is dependent upon the maintenance of normal basal glucagon levels;

inhibition of basal glucagon secretion causes a profound reduction in endogenous glucose production and a decline in plasma glucose concentration. On the other hand, hyperinsulinemia inhibits glucagon production, with subsequent suppression of hepatic glucose production and maintenance of normal postprandial glucose tolerance (9).

Epidemiology of diabetes

Type 1 diabetes

Type 1 diabetes is one of the most frequent chronic childhood diseases. According to the American Diabetes Association, this form is present in the 5–10% of patients with diabetes. Peak incidence occurs during puberty, around 10–12 years of age in girls and 12–14 years of age in boys. Siblings of children with type 1 diabetes have about a 10% chance of developing the disease by the age of 50 years. Identical twins have a 25–50% higher chance of developing type 1 diabetes than a child in an affected family. There is a higher incidence of type 1 diabetes in Caucasians than in other racial groups.

The incidence of childhood type 1 diabetes increased worldwide in the closing decades of the 20th century. Over the third to sixth decades of that century the incidence and prevalence of diabetes were low and relatively unchanged. Since 1950 a linear increase has been seen in Scandinavia, the UK, and the U.S. (58). Different etiologies have been proposed for the increased incidence and prevalence of type 1 diabetes, including early exposure to cow's milk. It has been suggested that a strong humoral response to the proteins in cow's milk may trigger the autoimmune process in young patients with type 1 diabetes, resulting in the destruction of the pancreatic β cells (72, 120). Another potential triggering event for autoimmune β -cell destruction is an abnormal response to an enterovirus infection (63). These environmental factors in type 1 diabetes are still poorly defined.

The incidence of type 1 diabetes is highest in Scandinavia, with more than 30 cases/year/100,000 people; of medium incidence in Europe and the U.S. (10–15 cases/year/100,000); and lower in Asian groups (0.5 cases/year/100,000) and in populations living in the tropics (78).

Type 2 diabetes

In the year 2000 the worldwide prevalence of type 2 diabetes was estimated to be 150 million people and

it is expected to increase to 220 million by 2010 (151). In the U.S. the prevalence is calculated to be approximately 16 million people with type 2 diabetes and an additional 30–40 million with impaired glucose tolerance (103). This disease has a varying prevalence among different ethnic groups. In the U.S. the most affected populations are Native Americans, particularly in the southwest, Hispanic-Americans and Asian-Americans (71).

Type 2 diabetes has a stronger genetic component than type 1, with a concordance rate of up to 90% in identical twins (107). While over 250 genes have been tested for possible relationships with type 2 diabetes, none has shown consistent associations in multiple study populations (59). In addition to genetic risk factors for type 2 diabetes, acquired or environmental factors play a major role; foremost among these is obesity.

The role of obesity in insulin resistance has been well established. A body mass index over 25 kg/m² is defined as overweight, and a body mass index of over 30 kg/m² is defined as obese. Obesity is the most common metabolic disease in developed nations. The World Health Organization (WHO) has estimated that worldwide there are more than one billion adults who are overweight, with at least 300 million of them being obese. Increased consumption of more energy-dense, nutrient-poor foods with high levels of sugar and saturated fats, combined with reduced physical activity, have led to obesity rates that have risen three-fold or more since 1980 in some areas of North America, the UK, Eastern Europe, the Middle East, the Pacific Islands, Australia and China. The obesity epidemic is not restricted to industrialized societies; this increase is often faster in developing countries than in the developed world (147). The prevalence continues to increase, with >30% of adults in the U.S. being obese and >60% of adults being overweight or obese (52).

Classification of diabetes mellitus

The American Diabetes Association issued new classification and diagnostic criteria for diabetes in 1997 (6). These criteria were modified in 2003 to include the diagnosis of impaired fasting glucose and impaired glucose tolerance (7).

Type 1 diabetes

This form of diabetes is the result of cellular-mediated immune β -cell destruction, usually leading to

total loss of insulin secretion. Type 1 diabetes is usually present in children and adolescents, although some studies have demonstrated 15–30% of all cases diagnosed after 30 years of age (91). In this older group of type 1 patients the β -cell destruction occurs more slowly than in children, with a less abrupt onset of symptoms. This demonstrates that the pace and extent of cellular destruction can occur at a different rate from patient to patient. Insulinopenia in patients with type 1 diabetes makes the use of exogenous insulin necessary to sustain life. In the absence of insulin these patients develop ketoacidosis, a life-threatening condition. This is why type 1 diabetes was previously called insulin-dependent diabetes, because type 1 patients are dependent on exogenous insulin for survival.

Markers of autoimmune destruction have been identified and can be used for diagnosis or risk assessment. These include antibodies to islet cells and to insulin, glutamic acid decarboxylase and tyrosine phosphatase IA-2 and IA-2 β (12). About 85–90% of patients can have one or more of these antibodies detected when diagnosed with type 1 diabetes.

Type 1 diabetes has a genetic predisposition with strong human leukocyte antigen associations, *DQA*, *DQB* and *DRB* genes. Monozygous twins have a concordance for type 1 diabetes of 30–50%. These patients are also prone to other autoimmune disorders such as Graves' disease, Hashimoto's thyroiditis, Addison's disease, vitiligo, celiac sprue, autoimmune hepatitis, myasthenia gravis, and pernicious anemia as part of the polyglandular autoimmune syndrome (40).

Idiopathic diabetes

Some forms of type 1 diabetes have no known etiologies. These patients have no evidence of autoimmunity, permanent insulinopenia and are prone to ketoacidosis. This only represents a minority of patients with type 1 diabetes and the majority of these patients are of African or Asian ancestry. This form of diabetes is strongly inherited, lacks immunological evidence for β -cell autoimmunity, and is not human leukocyte antigen-associated. An absolute requirement for insulin replacement therapy in affected patients may come and go.

Type 2 diabetes

This form of diabetes was previously defined as non-insulin-dependent diabetes. It is now known that type 2 diabetic patients have insulin resistance, which alters the utilization of endogenously pro-

duced insulin at the target cells. Type 2 patients have altered insulin production as well. In many patients, especially early in the disease, insulin production is increased, resulting in hyperinsulinemia. As the condition progresses, insulin production often decreases and patients have a relative insulin deficiency in association with peripheral insulin resistance (111). However, autoimmune destruction of β cells does not occur, and patients retain the capacity for some insulin production. This decreases the incidence of ketoacidosis in people with type 2 diabetes compared to those with type 1, but ketoacidosis can occur in association with the stress of another illness such as an infection.

Type 2 is the form of diabetes present in 90–95% of patients with the disease. At the beginning of the disease and often throughout their lifetime, these individuals do not need insulin treatment to survive. The primary abnormality is insulin resistance and the β -cell dysfunction arises from the prolonged, increased secretory demand placed on them by the insulin resistance. Insulin secretion is defective in these patients and insufficient to compensate for insulin resistance. They can remain undiagnosed for many years because the hyperglycemia appears gradually and many times without symptoms (28). Most patients with this form of diabetes are obese or may have an increased percentage of body fat distributed predominantly in the abdominal region. Adipose tissue plays an important role in the development of insulin resistance. Elevated circulating levels of free fatty acids derived from adipocytes have been demonstrated in numerous insulin resistance states. Free fatty acids contribute to insulin resistance by inhibiting glucose uptake, glycogen synthesis, and glycolysis, and by increasing hepatic glucose production (11).

Insulin resistance may improve with weight reduction and/or pharmacological treatment, but is seldom restored to normal. In addition to the strong genetic predisposition, which is still not clearly identified, the risk of developing this form of diabetes increases with age, obesity, previous history of gestational diabetes, and lack of physical activity.

Gestational diabetes mellitus

Gestational diabetes mellitus is defined as glucose intolerance, which is first recognized during pregnancy. It complicates 4% of all pregnancies in the U.S., resulting in 135,000 cases annually (45, 121). The prevalence may range from 1% to 14% of pregnancies, depending on the population studied. Gesta-

tional diabetes mellitus represents nearly 90% of all pregnancies complicated by diabetes; it usually has its onset in the third trimester of pregnancy and adequate treatment will reduce perinatal morbidity. Risk assessment for gestational diabetes mellitus should be performed at the first prenatal visit. Women at high risk are those older than 25 years of age, with positive family history of diabetes, previous personal history of gestational diabetes mellitus, marked obesity, and members of high-risk ethnic groups like African-Americans, Hispanics, and American Indians. Women from these groups should be screened as soon as possible. If the initial screening is negative, they should undergo retesting at 24–28 weeks. Women of average risk should have the initial screen performed at 24–28 weeks. At least 6 weeks after the pregnancy ends, the woman should receive an oral glucose tolerance test and be reclassified. Most women with gestational diabetes mellitus return to a normoglycemic state after parturition; however, a history of gestational diabetes mellitus markedly increases the risk for subsequently developing type 2 diabetes.

The diagnosis of gestational diabetes mellitus can represent an unidentified pre-existing diabetic condition, the unmasking of a compensated metabolic abnormality by the pregnancy, or a direct metabolic consequence of the hormonal changes. Under normal conditions, insulin secretion is increased by 1.5- to 2.5-fold during pregnancy, reflecting a state of insulin resistance (56). A woman with a limited β -cell reserve may be incapable of making the compensatory increase in insulin production required by her insulin-resistant state.

Women with gestational diabetes mellitus have an increased frequency of hypertensive disorders; furthermore, gestational diabetes mellitus increases the risk for fetal congenital abnormalities, stillbirth, macrosomia, hypoglycemia, jaundice, respiratory distress syndrome, polycythemia, and hypocalcemia (87).

Other specific types of diabetes

Genetic defects of the β cell

These conditions are associated with monogenetic defects in β -cell function. The onset of hyperglycemia is generally before the age of 25 years. They are referred to as maturity-onset diabetes of the young and are characterized by impaired insulin secretion with minimal or no defects in insulin action (10). These defects are inherited in an autosomal dominant pattern.

Genetic defects in insulin action

These are abnormalities associated with mutations of the insulin receptor and may range from hyperinsulinemia and modest hyperglycemia to severe diabetes. Some individuals with these mutations may have acanthosis nigricans. Women may be virilized (development of male sex characteristics in a female) and have enlarged, cystic ovaries.

Diseases of the exocrine pancreas

Any process that diffusely injures the pancreas can cause diabetes. Acquired processes include pancreatitis, trauma, infection, pancreatectomy, and pancreatic carcinoma. Also included in this type are cystic fibrosis and hemochromatosis.

Endocrinopathies

Acromegaly, Cushing's syndrome, glucagonoma, and pheochromocytoma can all cause diabetes.

Drug- or chemical-induced diabetes

This form of diabetes occurs with drugs or chemicals that affect insulin secretion, increase insulin resistance or permanently damage pancreatic β cells. A commonly encountered example is the patient taking long-term or high-dose steroid therapy for autoimmune diseases or post-organ transplantation, which can result in steroid-induced diabetes.

Infections

Viral infections that may cause β -cell destruction include coxsackievirus B, cytomegalovirus, adenovirus, and mumps.

Other genetic syndromes sometimes associated with diabetes

These include Down's syndrome, Klinefelter's syndrome, Turner's syndrome, and Wolfram syndrome.

Impaired glucose tolerance and impaired fasting glucose

It was previously recognized that there exists an intermediate group of individuals whose glucose levels, although not meeting the criteria for diabetes, were too high to be considered normal. Members of this group have a condition called 'pre-diabetes', a

Table 1. American Diabetes Association criteria for the diagnosis of diabetes mellitus, impaired glucose tolerance (IGT), and impaired fasting glucose (IFG)

| | Normal | Diabetes | IGT | IFG |
|-------------------------|--------|----------|----------------|---------|
| Fasting glucose (mg/dl) | <100 | ≥ 126 | | 100–125 |
| Casual glucose (mg/dl) | | ≥ 200 | | |
| 2-h PG* (mg/dl) | <140 | ≥ 200 | ≥ 140 but <200 | |

*2-h Post-loading glucose using the 2-h oral glucose tolerance test.

term which encompasses both impaired fasting glucose and impaired glucose tolerance. These patients are usually normoglycemic, but demonstrate elevated blood glucose levels under certain conditions (i.e. after fasting and after a glucose load for impaired fasting glucose and impaired glucose tolerance, respectively) (5) (Table 1). Both impaired fasting glucose and impaired glucose tolerance predict the future development of type 2 diabetes and impaired glucose tolerance is a strong predictor of myocardial infarction and stroke (27).

Diagnostic criteria

The level of blood glucose used for the diagnosis of diabetes and related conditions is based on the level of glucose above which microvascular complications have been shown to increase. The risk of developing retinopathy has been shown to increase when the fasting plasma glucose concentration exceeds 108–116 mg/dl (6.0–6.4 mmol/l), when the 2-h post-prandial level rises above 185 mg/dl (10.3 mmol/l), and when the hemoglobin A_{1c} level is greater than 5.9–6.0%.

The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus of the American Diabetes Association in 1997 revised the criteria for establishing the diagnosis of diabetes and the WHO adopted this change in 1998 (1, 6). To minimize the discrepancy between the fasting plasma glucose and 2-h post-prandial plasma glucose concentration measured during the oral glucose tolerance test, cut off values of ≥ 126 and ≥ 200 mg/dl, respectively, were chosen.

There are three ways to diagnose diabetes (5). If any of these criteria is found, it must be confirmed on a different day; that is, a single abnormal laboratory test is not sufficient to establish a diagnosis:

- symptoms of diabetes plus casual plasma glucose concentration ≥ 200 mg/dl (≥ 11.1 mmol/l). ‘Casual’ is defined as any time of day without regard to

time since the last meal. The classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss;

- fasting plasma glucose ≥ 126 mg/dl (≥ 7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 h;
- 2-h post-load glucose ≥ 200 mg/dl (≥ 11.1 mmol/l) during an oral glucose tolerance test. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.

The diagnosis of impaired glucose tolerance can only be made using the oral glucose tolerance test; it is diagnosed when the 2-h post-load plasma glucose concentration is ≥ 140 mg/dl but ≤ 199 mg/dl (between 7.8 and 11.1 mmol/l) (Table 1). Conversely, impaired fasting glucose is diagnosed after a fasting plasma glucose test and is defined by a plasma glucose ≥ 100 mg/dl but ≤ 125 mg/dl (between 5.6 and 6.9 mmol/l).

The hemoglobin A_{1c} test is used to monitor the overall glycemic control in people known to have diabetes. It is not recommended for diagnosis because there is not a ‘gold standard’ assay for hemoglobin A_{1c} and because many countries do not have ready access to the test.

Diagnosis of gestational diabetes mellitus

Carpenter and Coustan established the criteria for glucose intolerance in pregnancy using a 50-g oral glucose challenge test (17). Their criteria are supported by the American Diabetes Association, which also supports the alternative use of the 75-g anhydrous glucose 2-h oral glucose tolerance test described above (5).

The low-risk groups of patients who usually do not need to be screened for gestational diabetes mellitus are women who:

- are <25 years of age;
- have a normal body weight;
- have no family history (i.e. a first-degree relative) of diabetes;
- have no history of abnormal glucose metabolism;
- have no history of poor obstetric outcome;
- are not members of an ethnic/racial group with a high prevalence of diabetes (e.g. Hispanic-American, Native American, Asian-American, African-American, or Pacific Islander).

Women with a high risk of gestational diabetes mellitus should undergo glucose testing as soon as possible, with re-testing between 24 and 28 weeks of gestation. Women of average risk are usually tested for the first time at 24–28 weeks of gestation, and do not generally need re-testing if the initial screening is negative. Just as in a nonpregnant individual, a fasting plasma glucose level ≥ 126 mg/dl (7.0 mmol/l) or a casual plasma glucose ≥ 200 mg/dl (11.1 mmol/l) suggests the diagnosis of diabetes; the diagnosis must be confirmed on a subsequent day.

Screening is made by a 50-g oral glucose load challenge test measuring the plasma or serum glucose concentration 1 h afterwards. If the value is > 140 mg/dl (7.8 mmol/l) this identifies 80% of women with gestational diabetes mellitus, and the yield is further increased to 90% by using a cut-off of > 130 mg/dl (7.2 mmol/l).

The actual diagnosis of gestational diabetes mellitus is usually based on a 3-h oral glucose tolerance test in which a fasting blood sample is drawn after 8–14 h of fasting. This is immediately followed by giving a 100-g glucose load orally and then drawing blood samples again at 1, 2, and 3 h time-points. If two or more of the threshold glucose levels are exceeded the diagnosis is made (Table 2).

Table 2. Diagnosis of gestational diabetes mellitus with a 100-g glucose load in a 3-h oral glucose tolerance test

| Time | Plasma glucose |
|---------|--------------------------------|
| Fasting | ≥ 95 mg/dl (5.3 mmol/l) |
| 1 h | ≥ 180 mg/dl (10.0 mmol/l) |
| 2 h | ≥ 155 mg/dl (8.6 mmol/l) |
| 3 h | ≥ 140 mg/dl (7.8 mmol/l) |

Table 3. Signs and symptoms of undiagnosed diabetes

- Polyuria (excessive urination)
- Polydipsia (excessive thirst)
- Polyphagia (excessive hunger)
- Unexplained weight loss
- Changes in vision
- Fatigue, weakness
- Irritability
- Nausea
- Dry mouth
- Ketoacidosis*

*Ketoacidosis is usually associated with *severe* hyperglycemia and occurs mainly in type 1 diabetes.

Clinical presentation of diabetes (signs and symptoms)

Type 1 diabetes

The onset of type 1 diabetes is usually rather abrupt when compared to that of type 2. The classic signs and symptoms of diabetes are polyuria, polydipsia, and polyphagia; however, others may be present (99) (Table 3). Sustained hyperglycemia causes osmotic diuresis, leading to polyuria. This increased urination causes a loss of glucose, free water, and electrolytes in the urine, with consequent polydipsia. Postural hypotension may be present secondary to decreased plasma volume, and weakness can occur as a result of potassium wasting and catabolism of muscle proteins. Weight loss often takes place despite the patient's excessive sense of hunger (polyphagia) and frequent food intake. Blurred vision is a consequence of the exposure of the lens and retina to the hyperosmolar state.

If the insulin deficiency is acute, as often occurs in type 1 diabetes, these signs and symptoms develop abruptly. When ketoacidosis is present, greater hyperosmolarity and dehydration are present causing nausea, vomiting, and anorexia with various levels of altered consciousness.

Type 2 diabetes

Patients with type 2 diabetes can be initially asymptomatic or may have symptoms of polyuria and polydipsia. Others may present initially with pruritus or evidence of chronic or acute skin and mucosal infections such as candidal vulvovaginitis or intertrigo.

Typically, type 2 diabetic patients are obese and may present with neuropathic or cardiovascular complications, hypertension, or microalbuminuria. Because type 2 diabetes can remain undiagnosed for many years, these patients may have significant diabetic complications even at the time of initial diagnosis.

Assessment of metabolic (glycemic) control in diabetes

Since improvement in glycemic control is associated with a major decrease in the risk of diabetic complications, it is important to assure normal or near normal glucose levels. There are different tools to determine the level of glucose control, but a safe glycemic range must be considered for each patient, taking into account coexisting medical conditions, age of the patient, ability to follow a treatment program and possible presence of hypoglycemia unawareness.

Home blood glucose monitoring

Many different kinds of glucometers are now available on the market and almost all patients with diabetes have a glucometer at home. The data must be obtained in an organized manner taking into account the relationship between blood glucose and meal intake, insulin dose, physical activity, or coexisting illness. A small sterile lancet is used by the patient to make a puncture in the fingertip, and a drop of capillary blood is obtained and placed on a strip that is inserted in the glucometer. After a few seconds, the glucometer provides a blood glucose reading.

The glucometer is a very valuable tool, which provides the individual with a rapid assessment of his or her blood glucose level, helping to achieve normalization of blood glucose levels because a 24-h glucose profile can be obtained. Proper use of the glucometer also helps to ensure patient safety within treatment because the patient can obtain an immediate glucose reading should signs or symptoms of abnormal blood glucose levels arise.

Each diabetic patient requires a different treatment regimen, components of which may include diet, exercise, oral hypoglycemic agents, insulin-sensitizing agents, multiple insulin injections, or subcutaneous insulin pumps. All of these interventions can be modified depending on the different glucometer reading that the patient obtains.

Common causes of erroneous glucometer values include insufficient blood sample on the strip,

touching of the area on the test strip on which the sample is applied, moisture on the strips, inadequate cleaning of the device or improper machine calibration. Home glucose monitoring is mandatory in the management of gestational diabetes, and almost all type 1 diabetic patients use glucometers multiple times a day. Most type 2 patients also use glucometers, although they may not test their blood glucose as frequently as those with type 1.

Urine testing

Urine testing is rarely used for glucose control today. However, it can be helpful for patients unable to use a home glucose monitor. This method takes advantage of the patient's renal glucose threshold. For most patients, when the plasma glucose exceeds 180 mg/dl, glycosuria occurs. Presence of glucose in the urine is detected by the generation of color changes on urine reagent strips. Renal glucose thresholds vary from one person to another; therefore, blood testing for glucose levels is much more accurate than urine testing.

In contrast to urine glucose testing, use of urine ketone detection strips remains important in patient care. These strips detect ketone bodies (acetoacetic acid and acetone). Urinary ketones are commonly measured during the management of gestational diabetes, in which the goal is to have no ketones present in the urine. Ketone test strips are also used in type 1 diabetic patients with sustained hyperglycemia, allowing recognition of early development of diabetic ketoacidosis. For example, when the type 1 diabetic patient becomes ill, he or she will often test the urine for ketones. In addition to diabetes, other causes of ketoaciduria include starvation, hypocaloric diets, fasting, and alcoholic ketoacidosis.

Glycated hemoglobin (hemoglobin A_{1c})

Numerous proteins in the body are capable of being glycated. Glycohemoglobin is formed continuously in erythrocytes as a product of the non-enzymatic reaction between the hemoglobin protein, which carries oxygen molecules, and glucose. Binding of glucose to hemoglobin is highly stable; thus, hemoglobin remains glycated for the life span of the erythrocyte, approximately 123 ± 23 days (143). Determination of glycohemoglobin levels provides an estimate of the average blood glucose level over time, with higher average blood glucose levels reflected in higher hemoglobin A_{1c} values (Table 4) (112). Measurement of hemoglobin A_{1c} is of major clinical value

Table 4. Correlation between hemoglobin A_{1c} levels and mean plasma glucose levels

| HbA _{1c} (%) | Mean plasma glucose | |
|-----------------------|---------------------|--------|
| | mg/dl | mmol/l |
| 6 | 135 | 7.5 |
| 7 | 170 | 9.5 |
| 8 | 205 | 11.5 |
| 9 | 240 | 13.5 |
| 10 | 275 | 15.5 |
| 11 | 310 | 17.5 |
| 12 | 345 | 19.5 |

Hemoglobin A_{1c} provides an estimate of the average glucose level. It does not account for short-term fluctuation in plasma glucose levels.

and accurately reflects the mean blood glucose concentration over the preceding 1–3 months. Hemoglobin A_{1c} levels correlate well with the development of diabetic complications, and may in the future become established as a test for the diagnosis of diabetes (26).

It is generally recommended that the hemoglobin A_{1c} test is performed at least twice a year in patients who are meeting treatment goals, and every 3 months in patients whose therapy has changed or who are not meeting their glycemic goals. The recommended hemoglobin A_{1c} target value for people with diabetes is <7.0% (normal is <6%). Achieving this goal is difficult, and a recent population study showed that only 36% of people with type 2 diabetes achieved a target hemoglobin A_{1c} of <7.0% (90).

Fructosamine

There are other serum proteins beside hemoglobin that become glycosylated in the presence of hyperglycemia. Measurement of these glycosylated proteins can be used as an alternative to the HbA_{1c}. Albumin is a serum protein with a half-life of 2–3 weeks; measurement of glycosylated albumin reflects glycemic control over a shorter interval than does the hemoglobin A_{1c}. This can be helpful when an objective measurement that reflects a shorter period of time is needed, as might occur during initiation of a new therapy, during a medical illness, during pregnancy, or when the hemoglobin A_{1c} may not be reliable (for example, when anemia is present). The normal range for the fructosamine test is 2.0–2.8 mmol/l.

Acute complications of diabetes mellitus

Diabetic ketoacidosis

Diabetic ketoacidosis is the most common life-threatening hyperglycemic emergency in patients with diabetes and it is the leading cause of death in children with type 1 diabetes (18). Diabetic ketoacidosis may result from increased insulin requirements in type 1 patients during periods of physiological stress, such as infection, trauma, myocardial infarction, or surgery, and when psychological stress or poor compliance are present. While diabetic ketoacidosis is much less common in type 2 diabetes, it may develop under conditions of severe stress.

Diabetic ketoacidosis is a metabolic abnormality characterized by hyperglycemia and metabolic acidosis as a result of hyperketonemia with neurological manifestations (85). It is usually preceded by polyuria, polydipsia, fatigue, nausea, vomiting, and finally depression of sensorium and coma. Patients present with one or more of the following: hyperventilation (Kussmaul breathing), signs of dehydration, 'fruity' breath odor of acetone, hypotension, tachycardia, and hypothermia.

The treatment of diabetic ketoacidosis is performed on an inpatient basis, with very close monitoring of the patient (18). Management includes continuous intravenous infusion of regular (short-acting) insulin, which helps to correct the acidosis by reducing hyperglycemia, diminishing the flux of fatty acids to the liver, and decreasing ketone production (32). Fluid replacement should be initiated as soon as possible to improve circulatory volume and tissue perfusion. The fluid deficit is usually 4–5 l. Electrolyte replacement for potassium and phosphate is also required. It is important to keep in mind the identification and treatment of the underlying precipitating condition that triggered the diabetic ketoacidotic event.

The prevention of ketoacidosis is paramount in the education of the diabetic patient and includes early recognition of symptoms and signs, as well as measurement of urinary ketones when there is persistent hyperglycemia or in the event of infection. Patients also need to know the importance of compliance with diabetes management regimens for the prevention of diabetic ketoacidosis (86). Because diabetic ketoacidosis usually develops over several days or longer, it is less likely to occur acutely in the dental office, when compared to hypoglycemic emergencies.

Hyperglycemic hyperosmolar state

Hyperglycemic hyperosmolar state is the second most common life-threatening form of decompensated diabetes mellitus (86). The greatest risk is for elderly people, particularly those bedridden or dependent on others for their daily care. Infection is a common precipitating event, as is poor compliance with insulin therapy. Although there are many possible causes, the final common pathway is usually decreased access to water. Various drugs that alter carbohydrate metabolism, such as corticosteroids, pentamidine, sympathomimetic agents, β -adrenergic blockers, and excessive use of diuretics in the elderly may also precipitate the development of hyperglycemic hyperosmolar state. Presence of renal insufficiency and congestive heart failure worsen the prognosis.

Hyperglycemic hyperosmolar state is a metabolic abnormality characterized by severe hyperglycemia in the absence of significant ketosis, with hyperosmolarity and dehydration secondary to insulin deficiency, and massive glycosuria leading to excessive water loss (46). Hyperglycemic hyperosmolar state symptoms may occur more insidiously, with weakness, polyuria, polydipsia, and weight loss persisting for several days before hospital admission. In hyperglycemic hyperosmolar state, mental confusion, lethargy, and coma are more frequent because the majority of patients, by definition, are hyperosmolar. On physical examination, profound dehydration in a lethargic or comatose patient is the hallmark. Some patients present with focal neurological signs (hemiparesis or hemianopsia) and seizures.

Treatment of hyperglycemic hyperosmolar state consists of vigorous hydration, electrolyte replacement, and small amounts of insulin. Mortality rate is around 15% in hyperglycemic hyperosmolar state, and the risk is increased substantially with aging and the presence of a concomitant life-threatening illness. Most deaths occur in the first 2 days of hospitalization; thereafter, a significant decrease in morbidity and mortality is seen (93).

Hypoglycemia

Hypoglycemia is a common problem in diabetic patients and in the seriously ill patient because of the combination of medical conditions and the use of multiple medications, particularly insulin (23). Hypoglycemia is much more likely to be encountered in the dental office than are complications such as

diabetic ketoacidosis and hyperglycemic hyperosmolar state (100). Although the purpose of medical treatment in diabetes is to achieve a level of glycemic control that may prevent or delay the microvascular complications of the disease, the risk of hypoglycemia often precludes true glycemic control in patients with type 1 diabetes and many with type 2.

Many hypoglycemic episodes are never brought to medical attention because they are treated at home. However, severe hypoglycemia is a life-threatening event, and must be managed immediately. Hospitalization is required in a minority of patients, usually secondary to neurological manifestations such as seizures, lethargy, coma, or focal neurological signs.

Hypoglycemia is the result of absolute or relative therapeutic insulin excess and compromised glucose counter-regulation. Normally, as glucose levels fall insulin production decreases. In addition, glucagon is secreted from the pancreas, resulting in glycogenolysis and release of stored glucose from the liver. Epinephrine is also released from the adrenal medulla, causing further rise in blood glucose levels. Epinephrine release is responsible for many of the signs and symptoms often associated with hypoglycemia, such as shakiness, diaphoresis, and tachycardia (Table 5).

In some diabetic patients, especially those whose glucose levels are tightly controlled, the patient's physiological response to decreasing blood glucose levels becomes diminished over time. This phenomenon is known as hypoglycemia unawareness (61). Insulin levels do not decrease, epinephrine is not released, and glucagon levels do not increase, as they normally would be in response to falling glucose levels. Thus, a severe hypoglycemic event may occur with little or no warning. In studies examining the potential benefits of intensive diabetes management, the incidence of severe hypoglycemia was increased

Table 5. Signs and symptoms of hypoglycemia

- Confusion
- Shakiness, tremors
- Agitation
- Anxiety
- Diaphoresis
- Dizziness
- Tachycardia
- Feeling of 'impending doom'
- Seizures
- Loss of consciousness

Table 6. Risk factors for hypoglycemia in patients with diabetes

- Skipping or delaying meals
- Injection of too much insulin
- Exercise
 - Increasing exercise level without adjusting insulin or sulfonylurea dose
- Alcohol consumption
 - Inability to recognize symptoms of hypoglycemia
- Anxiety/stress
 - Patient may confuse signs of hypoglycemia with anxiety
- Denial of warning signs/symptoms
- Past history of hypoglycemia
- Hypoglycemia unawareness
- Good long-term glycemic control

Table 7. Treatment of hypoglycemia

- If patient is conscious and able to take food by mouth, give 15–20 g oral carbohydrate:
 - 4–6 oz (140–200 ml) fruit juice or soda, or
 - 3–4 teaspoons table sugar, or
 - hard candy or cake frosting equivalent to 15–20 g sugar
- If patient is unable to take food by mouth, and intravenous line is in place, give:
 - 30–40 ml 50% dextrose in water (D50), or
 - 1 mg glucagon
- If patient is unable to take food by mouth and intravenous line is *not* in place, give:
 - 1 mg glucagon subcutaneously or intramuscularly

three-fold in patients with excellent glycemic control (35, 36, 39). Furthermore, over one-third of hypoglycemic events in which the patient either required assistance from another person or became unconscious occurred with no warning. These facts serve to emphasize the importance of understanding the risk factors, signs, symptoms, and management of hypoglycemia (Table 5–7).

Treatment of a hypoglycemic event aims to elevate glucose levels to the point where signs and symptoms are resolved and glucose levels return to normal (Table 7). If the patient can take food by mouth, 15–20 g of carbohydrate are given orally. If the patient cannot take food by mouth and intravenous access is available, glucagon or 50% dextrose can be given. If intravenous access is not available, the drug

Table 8. Risk assessment for hypoglycemia. Questions to be asked by dentist to patient and/or patient's physician

- Have you ever had a severe hypoglycemic reaction before? Have you ever become unconscious or had seizures?
- How often do you have hypoglycemic reactions?
- How well controlled is your diabetes?
 - What were your last two hemoglobin A_{1c} values?
- What diabetic medication(s) do you take?
 - Did you take them today?
 - When did you take them? Is that the same time as usual?
 - How much of each medication did you take? Is this the same amount you normally take?
- What did you eat today before you came to the dental office?
 - What time did you eat? Is that when you normally eat?
 - Did you eat the same amount you normally eat for that meal?
 - Did you skip a meal?
- Do you have hypoglycemia unawareness?

of choice is glucagon because it can also be given intramuscularly or subcutaneously.

On every patient visit hypoglycemia must be addressed; the prevention of hypoglycemia in the diabetic patient is paramount (99). Physicians manage the risk of hypoglycemia by glycemic therapy adjustment and planning of food intake, reduction of insulin dose before exercise, and evaluating other risk factors such as age and coexisting medical conditions, including renal failure, gastroparesis, pregnancy, and other medications taken by the patient. Dentists can aid in risk assessment by asking specific questions related to past history of hypoglycemia, current level of glycemic control, and current medical regimen (Table 8).

Chronic macrovascular complications of diabetes mellitus

Cardiovascular disease

The risk of cardiovascular disease is markedly increased in patients with diabetes, and it is the major cause of mortality for these individuals. Cardiovascular disease is the most costly complication of diabetes and is the cause of 86% of deaths in people with diabetes. The term metabolic syndrome is used to describe a group of conditions which cluster to greatly

increase the risk of cardiovascular events: type 2 diabetes, abdominal obesity, insulin resistance, hypertension, and dyslipidemia (25, 132). The prevention or slowing of cardiovascular disease is achieved with the intervention of cardiovascular risk factors; these include blood pressure control, dyslipidemia treatment, smoking cessation, and aspirin therapy. Importantly, improved glycemic control has been shown to reduce the risk of cardiovascular events (38).

The prevalence of hypertension in the diabetic population is 1.5 to 3 times higher than that in non-diabetic age-matched groups, and there is evidence that diabetic individuals with hypertension have greatly increased risks of cardiovascular disease, renal insufficiency, and diabetic retinopathy. All patients with diabetes should have routine blood pressure measurements at each scheduled diabetes follow-up visit. Similarly, dentists should take blood pressure measurements routinely in this patient group. Diabetic patients with blood pressures >130 mmHg systolic or >80 mmHg diastolic are candidates for antihypertensive treatment aimed at lowering blood pressure to $<130/80$ mmHg. Initial pharmacological treatment includes drugs like angiotensin-converting enzyme inhibitors, α -adrenergic receptor blockers, low-dose thiazide diuretics, and β -blockers (8).

Patients with type 2 diabetes have an increased prevalence of lipid abnormalities that contributes to higher rates of cardiovascular disease. Lipid management aimed at lowering low-density lipoprotein cholesterol, raising high-density lipoprotein cholesterol, and lowering triglycerides has been shown to reduce macrovascular disease and mortality in patients with type 2 diabetes, particularly those who have had prior cardiovascular events (26). Lifestyle intervention must always be included and pharmacological intervention is indicated in these patients. Good glycemic control is also necessary to control hypertriglyceridemia.

Statins are the drug of choice for reduction of low-density lipoprotein and increase of high-density lipoprotein cholesterol. The Heart Protection Study demonstrated that in people over the age of 40 years with diabetes and a total cholesterol >135 mg/dl, a reduction of 30% in low-density lipoprotein levels following use of the statin drug simvastatin was associated with a 25% reduction in the first-event rate for major coronary artery events. This reduction in risk was independent of baseline low-density lipoprotein, pre-existing vascular disease, type or duration of diabetes, or adequacy of glycemic control (22). Similarly, in the Collaborative Atorvastatin Dia-

betes Study (CARDS), patients with type 2 diabetes randomized to atorvastatin 10 mg daily had a significant reduction in cardiovascular events including stroke (21).

For patients with diabetes over the age of 40 years with a total cholesterol >135 mg/dl but without overt cardiovascular disease, statin therapy to achieve a low-density lipoprotein reduction of 30–40% is recommended regardless of baseline low-density lipoprotein levels. The primary goal is a low-density lipoprotein <100 mg/dl (2.6 mmol/l). For individuals aged <40 years with diabetes, without overt cardiovascular disease, but at increased risk (because of other cardiovascular risk factors or long duration of diabetes), who do not achieve lipid goals with lifestyle modifications alone, the addition of pharmacological therapy is appropriate and the primary goal is a low-density lipoprotein cholesterol <100 mg/dl (2.6 mmol/l). People with diabetes and overt cardiovascular disease are at very high risk for further events and should be treated with a statin; if baseline low-density lipoprotein level is <100 mg/dl and the patient is considered to be at very high risk, initiation of a low-density lipoprotein-lowering drug to achieve a low-density lipoprotein level of <70 mg/dl is a therapeutic option that has clinical trial support (67).

The use of aspirin has been recommended as a primary and secondary therapy to prevent cardiovascular events in diabetic and nondiabetic individuals. Dosages used in most clinical trials ranged from 75 to 325 mg/day (3). There are consistent results from both cross-sectional and prospective studies showing enhanced risk for micro- and macrovascular disease, as well as premature mortality from the combination of smoking and diabetes (70). All diabetic patients must be advised not to smoke, and therapies for smoking cessation should be strongly recommended. Because smoking also has significant deleterious effects on oral health, the dentist is in a perfect position to serve as a smoking cessation advocate.

Chronic microvascular complications of diabetes mellitus

Nephropathy

Diabetic nephropathy occurs in 20–40% of patients with diabetes and is the leading cause of end-stage renal disease. This complication is more prevalent among African-Americans, Asians, and Native Americans than Caucasians, and there is a genetic

susceptibility that contributes to the development of nephropathy. The earliest clinical evidence of nephropathy is the appearance of low but abnormal levels (30 mg/day or 20 μ g/min) of albumin in the urine (64). With progressive disease and reduction in glomerular filtration capacity, macroalbuminuria may develop, with large amounts of protein excreted in the urine (proteinuria). Increased renal blood pressure may also occur. The mesangium, the membrane supporting the capillary loops in the renal glomeruli, expands as a result of increased production of mesangial matrix proteins. As the mesangium expands, the surface area for glomerular capillary filtration decreases, and the glomerular filtration rate declines. The expanding mesangium, combined with thickening of capillary basement membranes, renal hypertension, and declining glomerular filtration rate may then progress to end-stage renal disease.

Screening for microalbuminuria is performed on a spot urine sample using the albumin-to-creatinine ratio and should be performed every year, starting 5 years after diagnosis in type 1 diabetes. In patients with type 2 diabetes, screening should be performed at diagnosis and yearly thereafter. Patients with micro- and macroalbuminuria should undergo an evaluation regarding the presence of comorbid associations, especially retinopathy and macrovascular disease. Glycemic control, aggressive antihypertensive treatment using drugs with blockade effect on the renin–angiotensin–aldosterone system, and treating dyslipidemia are effective strategies for preventing the development of microalbuminuria. These therapies are effective in delaying the progression to more advanced stages of nephropathy and in reducing cardiovascular mortality in patients with type 1 and type 2 diabetes. Blood pressure goals during antihypertensive therapy are <130/80 mmHg, or <125/75 mmHg if the patient has proteinuria > 1.0 g/24 h and increased serum creatinine. The major goal for cholesterol management is a low-density lipoprotein cholesterol <100 mg/dl, or lower in some patients (64, 104).

Retinopathy

Diabetic retinopathy is the most frequent cause of new cases of blindness among adults aged 20–74 years. The duration of diabetes is probably the strongest predictor for development and progression of retinopathy. Eye examination should be performed annually and may need to be performed more frequently if retinopathy is progressing. Diabetic retin-

opathy progresses from mild nonproliferative abnormalities, characterized by increased vascular permeability, to moderate and severe nonproliferative diabetic retinopathy, characterized by vascular closure, and then to proliferative diabetic retinopathy, characterized by the growth of new blood vessels on the retina and posterior surface of the vitreous (13). Large intervention trials of both type 1 and type 2 diabetes clearly demonstrate that improved glycemia and blood pressure control can prevent and delay the progression of diabetic retinopathy in patients with diabetes (37, 108, 138). Timely laser photocoagulation therapy can also prevent loss of vision and macular edema (53).

Neuropathy

Neuropathy is a common complication of both type 1 and type 2 diabetes, with predominantly small-fiber involvement beginning at the distal extremities and progressively becoming more proximal with time and duration of diabetes. ‘Burning’ or ‘prickly’ feet are common descriptions from diabetic neuropathy patients. Recognition of neuropathy is very important because it represents an independent risk factor for ulcers of the skin and amputations. Diabetic neuropathy causes loss of protective sensation and alteration of biomechanics, which are associated with the increased risk of limb amputation (80).

Diabetic autonomic neuropathy has been associated with increased risk of cardiovascular mortality and multiple other symptoms and impairments. Clinical manifestations include resting tachycardia, exercise intolerance, orthostatic hypotension, constipation, gastroparesis (delayed gastric emptying), erectile dysfunction, impaired neurovascular function, ‘brittle diabetes’, and hypoglycemic autonomic failure (142). Patients must be evaluated for this complication and identified. Further tests like heart-rate variability may be indicated.

Mononeuritis, inflammation of a single nerve, can also occur and is more prevalent in the older population (141). Mononeuritis usually has an acute onset of pain. The course is generally self-limiting, resolving within 6–8 weeks. Most cases of mononeuritis are the result of vascular obstruction, after which adjacent neuronal fascicles take over the function of those infarcted by the clot.

All individuals with diabetes should receive an annual foot examination to identify high-risk foot conditions. Evaluation of neurological status in the low-risk foot includes a quantitative somatosensory threshold test, using the Semmes–Weinstein 5.07

(10-g) monofilament and vibration testing using a 128-Hz tuning fork. Once neuropathy is diagnosed, therapy can be instituted with the goal of both ameliorating symptoms and preventing the progression of neuropathy. Patients identified with peripheral neuropathy may be adequately managed with well-fitted walking shoes, and should be educated on the implications of sensory loss and the importance of manual palpation and visual inspection for surveillance of early problems. Patients also need gait and strength training, along with pain management and specific treatment for the different manifestations of diabetic neuropathy (4). As with microvascular complications such as retinopathy and nephropathy, longitudinal studies demonstrate a significant reduction in the risk of neuropathy in both type 1 and type 2 diabetic individuals with excellent glycemic control (36, 108, 138).

Pathways of diabetic complications

Inflammation and diabetes mellitus

Inflammation is significantly pronounced in the presence of diabetes, insulin resistance and hyperglycemia. There is growing evidence that obesity has major pro-inflammatory effects, which cause chronic activation of the innate immune system and play an important role in alterations of glucose tolerance (110). Various studies have demonstrated the elevated production of inflammatory products in these patients and the association with other risk factors. Subclinical inflammation has been linked as a risk factor for cardiovascular disease (50). High serum levels of the acute-phase reactants fibrinogen and C-reactive protein have been found in people with insulin resistance and obesity (51, 69). The inflammatory response in large vessels involves the up-regulation of pro-inflammatory cytokines, such as tumor necrosis factor- α , interleukin-1, and interleukin-6, and vascular adhesion molecules such as vascular cell adhesion molecule 1 and E-selectin. Pro-inflammatory cytokines amplify the inflammatory response, in part, by stimulating the expression of chemokines such as monocyte chemoattractant protein 1 and macrophage inflammatory protein 1 that direct the migration of leukocytes into the vessel wall (60). Activation of interleukin-18 has been found to be involved in the pathogenesis of the metabolic syndrome. Interleukin-18 is a pleiotropic pro-inflammatory cytokine with important regulatory functions in the innate immune response (76).

Higher levels of inflammatory indexes and adhesion molecules are detected in patients with diabetes and coronary artery disease, compared with nondiabetic patients with coronary artery disease and healthy control subjects. These higher levels are implicated in the prognosis of cardiovascular disease (122). Patients with diabetes have elevated local arterial heat generation during coronary thermography, indicative of increased inflammation in the arterial wall, when compared to nondiabetic subjects (136).

Insulin resistance is present in almost 70% of women with polycystic ovary syndrome. These women are often obese and hyperinsulinemia is considered to play a role in the hyperandrogenism (virilization) seen in these individuals. Polycystic ovary syndrome is a pro-inflammatory state as evidenced by elevated plasma concentrations of C-reactive protein, and low-grade chronic inflammation has been proposed as a mechanism contributing to increased risk of coronary heart disease and type 2 diabetes in these women (14, 81).

Obesity constitutes a low-grade chronic inflammatory state. An increased body mass index is associated with an increase in the size and number of adipocytes. Adipocytes have a high level of metabolic activity and produce large quantities of tumor necrosis factor- α and interleukin-6. In fact, about one-third of the circulating level of interleukin-6 is produced in adipose tissue (102). Obese individuals have elevated production of tumor necrosis factor- α and interleukin-6, and these increases are important in the pathogenesis of insulin resistance (51). Tumor necrosis factor- α is the major cytokine responsible for inducing insulin resistance at the receptor level. Tumor necrosis factor- α prevents autophosphorylation of the insulin receptor and inhibits second messenger signaling via inhibition of the enzyme tyrosine kinase (50). Interleukin-6 is important in stimulating tumor necrosis factor- α production; therefore, elevated interleukin-6 production in obesity results in higher circulating levels of both interleukin-6 and tumor necrosis factor- α . The increased cytokine levels also lead to increased C-reactive protein production, which may impact insulin resistance as well.

Recent years have seen an increased appreciation of the role systemic inflammation plays in the pathophysiology of diabetes and its complications. Research is ongoing into the potential sources of elevated systemic inflammatory states, including the potential for inflammation in localized sites such as the periodontium to have widespread effects.

Advanced glycation end-product formation

In people with sustained hyperglycemia, proteins become glycosylated to form advanced glycation end-products (15, 105). Formation of these stable carbohydrate-containing proteins is a major link between the various diabetic complications. Advanced glycation end-products form on collagen, a major component of the extracellular matrix throughout the body (105). In the blood vessel wall, advanced-glycation-end-product-modified collagen accumulates, thickening the vessel wall and narrowing the lumen. This modified vascular collagen can immobilize and covalently cross-link circulating low-density lipoprotein, causing an accumulation of low-density lipoprotein and contributing to atheroma formation in the large blood vessels. Advanced glycation end-product formation occurs in both central and peripheral arteries, and is thought to contribute greatly to macrovascular complications of diabetes, in part by up-regulation of vascular adhesion molecules. Modification of collagen by advanced glycation end-products also occurs in the basement membrane of small blood vessels, increasing basement membrane thickness and altering normal homeostatic transport across the membrane.

Advanced glycation end-products have significant effects at the cellular level, affecting cell-cell, cell-matrix, and matrix-matrix interactions. A receptor for advanced glycation end-products (known as RAGE) is found on the surface of smooth muscle cells, endothelial cells, neurons, monocytes, and macrophages (123, 125, 144). Hyperglycemia results in increased expression of this receptor for advanced glycation end-products and increased interactions between the advanced glycation end-products and their receptor on endothelium, causing an increase in vascular permeability and thrombus formation (49). These interactions on the cell surface of monocytes induce increased cellular oxidant stress and activate the transcription factor nuclear factor- κ B, altering the phenotype of the monocyte/macrophage and resulting in increased production of pro-inflammatory cytokines such as interleukin-1 and tumor necrosis factor- α (125). These cytokines contribute to chronic inflammatory processes in formation of atheromatous lesions (113).

Current medical management of diabetes mellitus

Worldwide, diabetes is a major growing public health problem, not only because of the health costs, which

exceed 100 billion dollars annually in the U.S., but also because of the widespread morbidity and mortality associated with the disease. Diabetes is actually a group of metabolic disturbances involving altered metabolism of carbohydrates, proteins, and lipids. Treatment of diabetes includes not only the normalization of glycemia, but interventions to prevent initiation of complications or their progression.

Diet

Dietary recommendations are widely recognized as a pivotal intervention in the treatment of diabetes. The goals of this intervention include weight reduction, improved glycemic control, with blood glucose levels in the normal range, and lipid control (54). Dietary interventions may reduce the likelihood of developing microvascular and macrovascular complications, and improve the quality of life and sense of well-being.

The recommended daily intake of carbohydrates for patients with diabetes is approximately 55–60% of total caloric intake (128). The total amount of carbohydrates in each meal is more important for glycemic effect than the specific source or type of carbohydrate. Whole grains, fruits, vegetables and low-fat milk should be included in a healthy diet. Intake of fat should be limited to approximately 30%. If the patient has dyslipidemia, saturated fat should be limited and should be replaced by polyunsaturated or monounsaturated fat, especially omega-3 fatty acids. Protein intake should be limited to 10–20% of total caloric intake.

There is no clear evidence of benefit from vitamin or mineral supplementation in people with diabetes who do not have underlying deficiencies. Exceptions include folate for prevention of birth defects and calcium for prevention of bone disease. Daily alcohol intake should be limited to one drink for adult women and two drinks for adult men. One drink is defined as a 12-oz beer (ca 400 ml), a 5-oz glass of wine (ca 170 ml), or 1.5-oz glass of distilled spirits (ca 50 ml). Alcohol should be consumed with food (54, 55).

Exercise

Regular physical exercise is an important component in the treatment of diabetes because several benefits have been identified in addition to weight reduction, increased cardiovascular fitness, and physical working capacity. Moderate intensity exercise is associated with a decrease in glycemia, as well as lower

fasting and post-prandial insulin concentrations, and increased insulin sensitivity. These changes are achieved through increases in insulin-sensitive glucose transporters (i.e. GLUT-4) in muscle, increases in the blood flow to insulin-sensitive tissues, and reduced free fatty acids (47). No less important for the diabetic population is the reduction in cardiovascular risk factors through improvement of the lipid profile and improvement in high blood pressure seen with regular exercise.

The Diabetes Prevention Program involved over 3,200 subjects with impaired fasting glucose/impaired glucose tolerance and obesity who were managed with placebo, metformin, or intensive lifestyle changes during an average follow-up time of approximately 3 years (88). Lifestyle changes, including diet and exercise, had a goal of 150 min of physical activity per week and a loss of 7% of body weight. Compared to the placebo group, those taking metformin had a 31% reduction in the incidence of type 2 diabetes, while those undertaking lifestyle changes experienced a 58% reduction. In addition to a reduced incidence of diabetes, the beneficial effects of an intensive lifestyle intervention included a 30% reduction in C-reactive protein levels, once again demonstrating that obesity is associated with elevated systemic inflammation, while weight loss and exercise can reduce the systemic inflammatory burden. In fact, the 30% reduction in C-reactive protein occurred despite only a modest 7% decline in weight achieved at 6 months (69).

Before beginning an exercise program, the patient with diabetes should undergo medical evaluation and, if necessary, appropriate diagnostic studies. Careful screening for the presence of macrovascular and microvascular complications that may be worsened by the exercise program must be done, and from that evaluation a tailored exercise program can be implemented (131). Patients with known coronary artery disease should undergo an evaluation for ischemia and arrhythmia during exercise. Evaluation of peripheral arterial disease includes asking the patient for signs and symptoms, such as intermittent claudication, cold feet, decreased or absent pulses, atrophy of subcutaneous tissues, and hair loss. Eye examination is important and for patients with active proliferative diabetic retinopathy, strenuous activity may precipitate vitreous hemorrhage or traction retinal detachment. These individuals should avoid anaerobic exercise and exercise that involves Valsalva-like maneuvers.

Peripheral neuropathy may result in a loss of protective sensation in the feet and is an indication to

limit weight-bearing exercise. Repetitive exercise on insensitive feet can ultimately lead to ulceration and fractures. The presence of autonomic neuropathy may limit an individual's exercise capacity and increase the risk of an adverse cardiovascular event during exercise (142). Hypotension and hypertension after vigorous exercise are more likely to develop in people with autonomic neuropathy, and because of altered thermoregulation they should be advised to avoid exercise in hot or cold environments and to be vigilant about adequate hydration.

The exercise program must be enjoyable and should include warm-up and cool-down periods. Hydration must be assured; it is recommended to ingest 17 oz of fluid (ca 580 ml) within the 2 h before exercise and to continue hydration during exercise. The therapeutic regimen must be adjusted for the amount of exercise that is planned to avoid hypoglycemia. For example, the insulin absorption rate increases markedly if the insulin is injected into a large muscle mass like the thigh muscle before or immediately after exercise. In such cases, hypoglycemia may occur as the insulin is rapidly absorbed and glucose is quickly transferred from the bloodstream into the tissues. Blood glucose must always be checked before beginning exercise.

Pharmacological therapy

Several studies have demonstrated the importance of pharmacological intervention for glucose control to decrease the development of microvascular and macrovascular complications. The Diabetes Control and Complications Trial established that in type 1 diabetes, the risk for microvascular complications could be reduced by maintaining near-normal blood glucose levels with intensive insulin therapy (36). Over 1,400 subjects with type 1 diabetes were either treated with conventional insulin therapy, consisting of one or two injections daily, or with intensive therapy, involving three or four injections a day (or use of an insulin pump). Intensive therapy significantly reduced the risk of the onset and progression of diabetic complications in this longitudinal study. As the hemoglobin A_{1c} value was reduced to less than 8.0%, the risk for microvascular complications continued to decrease. The Diabetes Control and Complications Trial results are applicable to type 2 diabetes as well, because retinal, renal, and neurological anatomical lesions seem to be identical in type 1 and type 2 diabetes, and epidemiological studies have shown a close association between

glycemic control and microvascular complications. It is clear that reduction of the plasma glucose level reduces microalbuminuria and improves nerve conduction velocity in patients with type 2 diabetes (108).

The United Kingdom Prospective Diabetes Study also showed a relationship between glycemic control and prevention of complications in type 2 diabetes (138). After a dietary run-in period of 3 months, 3,867 patients with newly diagnosed type 2 diabetes were randomly assigned to intensive therapy with a sulfonylurea or insulin ($n = 2,729$), or to conventional diet therapy ($n = 1,138$). In the intensive therapy group, the aim was to achieve a fasting plasma glucose level <6 mmol/l (108 mg/dl). In the sulfonylurea group, patients were switched to insulin therapy or metformin was added if the therapeutic goal was not achieved after maximum titration of the sulfonylurea drug dose. In patients assigned to insulin treatment in which the therapeutic goal was not met, the dose of ultralente insulin was increased progressively and regular insulin was added. In patients assigned to conventional diet treatment, the aim was to maintain a fasting plasma glucose level <15 mmol/l (270 mg/dl) without symptoms. If the fasting plasma glucose level exceeded 15 mmol/l (270 mg/dl) or symptoms occurred, patients were randomly assigned to receive therapy with a sulfonylurea or insulin. The median follow-up was 10.0 years; during this period, a difference in hemoglobin A_{1c} values of 0.9% (7.0% compared with 7.9%; $P < 0.001$) was maintained between the group assigned to intensive therapy and the group assigned to conventional therapy, respectively. This difference was associated with a significant 25% risk reduction ($P = 0.009$) in combined microvascular end points (eye, kidney, and nerve) compared with the conventionally treated group. No significant difference in combined macrovascular end-points between the two groups was observed, although there was a tendency towards fewer myocardial infarctions in the group assigned to intensive therapy. In addition to the 2,729 patients with type 2 diabetes assigned to intensive therapy and the 1,138 patients assigned to conventional therapy, 342 overweight patients were randomly assigned to intensive treatment with metformin (139). These 342 patients were compared with 411 overweight diabetic patients receiving conventional therapy and with 951 overweight diabetic patients receiving intensive therapy (of whom 542 were receiving sulfonylureas and 409 were receiving insulin). The median follow-up in this group was 10.7 years; during this time, a difference in the hemoglobin A_{1c} value of 0.6% (7.4% compared

with 8.0%; $P < 0.001$) was maintained between the group assigned to metformin therapy and the group assigned to conventional therapy, respectively. The magnitude of reduction (29%) in the risk for microvascular complications in the metformin-treated group was similar to that in patients treated intensively with insulin or sulfonylureas, but it did not reach statistical significance. Patients assigned to intensive blood glucose control with metformin had a 32% lower risk ($P = 0.002$) for any diabetes-related end-point, a 36% lower risk ($P = 0.011$) for death from any cause, a 42% reduction in diabetes-related death ($P = 0.017$), a 39% lower risk ($P = 0.010$) for myocardial infarction, and a 41% lower risk ($P = 0.032$) for stroke compared with patients who received conventional treatment. The risk reduction for any diabetes-related end-point ($P = 0.003$) and death from any cause ($P = 0.021$) in the metformin group was significantly greater than that in the group assigned to intensive therapy with insulin or sulfonylureas.

A 6-year study in Japanese type 2 diabetic subjects showed that multiple daily insulin injections significantly reduced the onset and progression of retinopathy, nephropathy and neuropathy, when compared to conventional insulin injection (108). Onset of diabetic retinopathy occurred in 7.7% of the multiple injection group, compared to 32% in the conventional group. Onset of nephropathy occurred in 7.7% of multiple insulin injection patients, but in 28% of subjects in the conventional group. In subjects who already had early retinopathy at the baseline examination, progression of the condition occurred in 19% of intensively managed patients, compared to 44% of conventionally controlled subjects. Early nephropathy showed progression in 11.5% of intensively managed patients, compared to 32% of the conventional control group. The authors of this study concluded that the glycemic threshold, which was associated with prevention of the onset or progression of microvascular complications, included a fasting blood glucose of <110 mg/dl, a 2-h post-prandial glucose level of <180 mg/dl and a hemoglobin A_{1c} value of $<6.5\%$.

In type 2 diabetes, pharmacological therapy generally begins with an oral agent or insulin, and titration is adjusted frequently to rapidly achieve glucose control. If one agent is not adequate, another agent must be added.

Insulin therapy

Insulin therapy is indicated for all patients with type 1 diabetes. Insulin is also used in type 2 diabetic

patients with insulinopenia in whom diet and oral agents are inadequate to attain target glycemic control. Insulin therapy is also indicated for women with gestational diabetes mellitus who are not controlled with diet alone. Therapy is usually initiated with a single dose of long-acting insulin, and multiple split-dose regimens using rapid or short-acting insulin before meals are then added.

Insulin administered via subcutaneous injection is absorbed directly into the bloodstream; there are different factors that can affect absorption such as blood flow at the injection site, temperature, location of injection, or exercise. Side-effects of insulin include increased risk of hypoglycemia and weight gain from increased truncal fat. In fact, patients taking insulin have the greatest risk of hypoglycemia (36). True allergic reactions and cutaneous reactions to insulin are rare, because most insulins in use today are recombinant human products (74). To avoid lipohypertrophy, patients are instructed to rotate their insulin injection sites.

Insulin preparations differ markedly in their pharmacokinetic and pharmacodynamic properties (74). Standard insulin preparations include regular insulin, neutral protamine Hagedorn (NPH) insulin, zinc insulin (Lente) and extended zinc insulin (Ultralente) (Table 9). The standard preparations have relatively limited pharmacodynamic and pharmacokinetic properties, which lead to more frequent hypoglycemia when used in regimens targeted to achieve hemoglobin A_{1c} values approaching the normal range. For this reason, insulin analogs have been developed with action profiles that allow more flexible treatment regimens; these are associated with a lower risk of hypoglycemia. These analogs have either very short-acting (insulin lispro and insulin aspart) or very long-acting (insulin glargine) profiles (34) (Table 9). As a practical matter, clinicians should be

aware of the time of peak insulin action for each insulin preparation because the risk for hypoglycemia is usually highest at times of peak insulin action (see highlighted column in Table 9).

Insulin is usually administered as a bolus dose given subcutaneously with a syringe. Insulin pump or continuous subcutaneous insulin infusion therapy is another option for intensive insulin therapy. Insulin pumps are programmed to deliver small continuous basal doses of insulin throughout the day, with bolus dosing before meals. Insulin pump therapy was originally reserved for people with type 1 diabetes, but now some type 2 patients are using pumps. Pump patients need to be very knowledgeable about diabetes management, especially how to count carbohydrates and how to adjust their insulin doses. The advantages of insulin pumps include less weight gain, less hypoglycemia, and better control of fasting hyperglycemia.

Oral agents

Sulfonylureas (glipizide, glyburide, glimepiride)

The mechanism of action of the sulfonylurea agents is enhancement of insulin secretion by binding to a specific sulfonylurea receptor on pancreatic β cells. This closes a potassium-dependent adenosine triphosphate channel, leading to decreased potassium influx and depolarization of the β -cell membrane. This results in increased calcium flux into the β cell, activating a cytoskeletal system that causes translocation of secretory granules to the cell surface and extrusion of insulin through exocytosis (130). These medications must be started with the lowest effective dose and titrated upward every 1–2 weeks until the

Table 9. Insulin preparations*

| Insulin | Onset of action | Peak action | Effective duration |
|------------------|-----------------|------------------------|--------------------|
| Insulin Lispro | 5–15 min | 30–90 min | 4–6 h |
| Insulin Aspart | 5–15 min | 30–90 min | 4–6 h |
| Regular | 30–60 min | 2–3 h | 8–10 h |
| NPH | 2–4 h | 4–10 | 12–18 h |
| Lente | 2–4 h | 4–12 h | 12–20 h |
| Ultralente | 6–10 h | 14–16 h | 18–24 h |
| Insulin Glargine | 2–4 h | None (peakless) | 20–24 h |

*There are large individual variations within and between patients in insulin action. Data are from DeWitt and Hirsch (34).

Table 10. Oral agents for diabetes management

| Agent | Action | Risk of hypoglycemia |
|---|--|-----------------------------|
| Sulfonylureas | | |
| Glyburide | Stimulate pancreatic insulin secretion | High |
| Glipizide | | High |
| Glimepiride | | Moderate |
| Meglitinides | | |
| Repaglinide | Stimulate rapid pancreatic insulin secretion in presence of glucose | Low to moderate |
| Nateglinide | | Low to moderate |
| Biguanides: metformin | | |
| | Block production of glucose by liver; improve tissue sensitivity to insulin | Very low |
| Thiazolidinediones | | |
| Rosiglitazone | Improve tissue sensitivity to insulin | Very low |
| Pioglitazone | | Very low |
| α-Glucosidase inhibitors | | |
| Acarbose | Slow absorption of carbohydrate from gut; decrease post-prandial peaks in glycemia | Low |
| Miglitol | | Low |
| Combination agents | | |
| Metformin combined with glyburide | Combine actions from two different drug classes, as described above | Moderate (due to glyburide) |
| Metformin combined with glipizide | | Moderate (due to glipizide) |
| Metformin combined with rosiglitazone | | Very low |

desired control is achieved. In patients with type 2 diabetes the fasting plasma glucose level will generally decrease by 60–70 mg/dl (3.3–3.9 mmol/l) and the hemoglobin A_{1c} value will usually decrease by 1.5–2.0%. About 75% of patients treated with a sulfonylurea will not be at goal and will require the addition of a second oral agent or bedtime insulin. All the sulfonylureas have comparable glucose lowering potency (82). They differ in their pharmacodynamics and pharmacokinetics, with each having its own onset, peak, and duration of action. As the drug reaches peak activity, stimulation of pancreatic insulin secretion is at its highest. These drugs can cause hypoglycemia if there is insufficient glucose in the bloodstream at the time of peak activity (Table 10). Weight gain is another potential side-effect of the sulfonylureas.

Meglitinides (repaglinide, nateglinide)

The meglitinides are non-sulfonylurea insulin secretagogues that require the presence of glucose for their action and work by closing an adenosine

triphosphatase-dependent potassium channel (57). They are unique in that they have a rapid onset but short duration of action, stimulating a brief release of insulin. Thus, the meglitinides are given before meals. Insulin secretion rises rapidly to coincide with the rise in blood glucose that occurs as carbohydrate is absorbed from the gut. These medications generally decrease the hemoglobin A_{1c} value by 1.7–1.8% from baseline, and they have no significant effect on plasma lipid levels (62). Side-effects include weight gain and occasional hypoglycemia, although the risk of hypoglycemia is considerably lower than with sulfonylureas.

Biguanides (metformin)

Metformin is a second-generation biguanide that decreases blood glucose levels by decreasing hepatic glucose production (inhibition of gluconeogenesis) and decreasing peripheral insulin resistance. The mechanism of action appears to be mainly at the hepatocyte mitochondria, where metformin interferes with intracellular handling of calcium,

decreasing gluconeogenesis and increasing expression of glucose transporters (84). Metformin induces increases in adenosine monophosphate-activated protein kinase activity that are associated with higher rates of glucose disposal and muscle glycogen concentrations (106). The Diabetes Prevention Program showed that in people with impaired glucose tolerance or impaired fasting glucose, metformin reduced the incidence of type 2 diabetes by 31% (88). When used as a monotherapy, metformin decreases the fasting plasma glucose level by 60–70 mg/dl (3.3–3.9 mmol/l) and the hemoglobin A_{1c} by 1.5–2.0%. Metformin decreases plasma triglyceride and low-density lipoprotein cholesterol levels by 10–15%, and high-density lipoprotein cholesterol levels either do not change or increase slightly after metformin therapy. Serum plasminogen activator inhibitor-1 levels, which are often increased in type 2 diabetes, are decreased by metformin. Metformin does not promote weight gain. Because metformin does not alter insulin secretion, it is associated with a very low risk of hypoglycemia.

Metformin is usually started at a dosage of 500 mg twice daily, taken with the two largest meals to minimize gastrointestinal intolerance. The dose is increased by 500 mg/day every week to achieve the target glycemic control. The maximum dosage is 2000 mg/day. Adverse effects include abdominal discomfort and diarrhea. Lactic acidosis has been reported in some instances. Contraindications include renal dysfunction, hepatic dysfunction, hypoxemic conditions, severe infection and alcohol abuse (84).

Thiazolidinediones (rosiglitazone, pioglitazone)

The thiazolidinediones improve insulin sensitivity and are thus very useful in people with type 2 diabetes whose basic pathophysiological defect is insulin resistance. The peroxisome-proliferator-activated receptors are a subfamily of the 48-member nuclear-receptor superfamily and regulate gene expression in response to ligand binding. Peroxisome-proliferator-activated receptor- γ is a transcription factor activated by thiazolidinediones (146). In transactivation, which is DNA-dependent, peroxisome-proliferator-activated receptor- γ forms a heterodimer with the retinoid X receptor and recognizes specific DNA response elements in the promoter region of target genes. This ultimately results in transcription of peroxisome-proliferator-activated receptor- γ target genes. Perox-

isome-proliferator-activated receptor- γ is expressed mainly in adipose tissue, where it regulates genes involved in adipocyte differentiation, fatty acid uptake and storage, and glucose uptake. It is also found in pancreatic β cells, vascular endothelium, and macrophages.

Thiazolidinediones act as insulin sensitizers in the muscle and decrease hepatic fat content (148). Decreases in triglyceride levels have been observed more often with pioglitazone than with rosiglitazone. At maximal doses, these drugs decrease hemoglobin A_{1c} by 1.0–1.5%. Adverse effects include increase in body weight, fluid retention, and plasma volume expansion, and slight decreases in the hemoglobin level. Thiazolidinediones can cause hepatotoxicity, and measurements of transaminases must be performed periodically. Thiazolidinediones are rarely associated with hypoglycemia.

α -Glucosidase inhibitors (acarbose, miglitol)

These medications competitively inhibit the ability of enzymes (maltase, isomaltase, sucrase, and glucoamylase) in the small intestinal brush border to break down oligosaccharides and disaccharides into monosaccharides (92). By delaying the digestion of carbohydrates, but not by malabsorption, α -glucosidase inhibitors shift carbohydrate absorption to more distal parts of the small intestine and colon, and slow glucose entry into the systemic circulation. This allows the β cell more time to increase insulin secretion in response to the increase in plasma glucose level.

α -Glucosidase inhibitors decrease the fasting plasma glucose level by 25–30 mg/dl (1.4–1.7 mmol/l) and the hemoglobin A_{1c} value by 0.7–1.0% (19). Side-effects include bloating, abdominal discomfort, diarrhea, and flatulence. These agents do not induce hypoglycemia. However, because they slow down the absorption of carbohydrates from the intestine, they can alter the required timing or dose of other medications such as insulin or meglitinides.

Combination oral agents

Drug manufacturers have recently begun marketing combination oral agents. These drugs combine metformin with either a sulfonylurea (glipizide or glyburide) or a thiazolidinedione (rosiglitazone). Because sulfonylureas are associated with potential hypoglycemia, combination agents containing sulfo-

nylureas carry some risk. The combination agent containing rosiglitazone has minimal risk for hypoglycemia.

Newly approved agents for diabetes

Pramlintide, Amylin analog (Symlin®)

Within the past few years, new agents have come on the market for diabetes management (140). Pramlintide, approved by the Food and Drug Administration in 2005, is an antihyperglycemic drug for use in diabetic patients who are also being treated with insulin. Pramlintide is a synthetic analog of the hormone amylin (126). Normally, amylin is produced in the β cells of the pancreas and is packaged along with insulin for secretion. It modulates gastric emptying, prevents the post-prandial rise in plasma glucagon, and produces satiety, leading to decreased caloric intake and weight loss. In type 1 diabetes, destruction of pancreatic β cells eliminates the production of both insulin and amylin. Injection of pramlintide decreases post-prandial glucose elevations and decreases cellular oxidative stress, a major cause of diabetic complications.

Meal-time pramlintide treatment as an adjunct to insulin-improved long-term glycemic control without inducing weight gain in type 1 diabetic patients. It can also be used as an adjunct to insulin therapy in patients with type 2 diabetes, improving long-term glycemic and weight control (75). Pramlintide was found to provide an average reduction in hemoglobin A_{1c} of 0.7% from baseline (145). It is given by subcutaneous injection twice a day (before large meals) in doses of 15, 30, 45, 60, 90, or 120 μ g. Pramlintide cannot be mixed with insulin, and must be injected separately. The major side-effect of pramlintide is hypoglycemia, which can be severe. The Food and Drug Administration requires that the package insert for pramlintide carry a 'black box warning', clearly identifying the high risk for hypoglycemia.

Exenatide (Byetta®)

Exendin-4 is an incretin hormone that was originally isolated from the salivary secretions of the lizard *Heloderma suspectum* (Gila monster). The drug exenatide (a synthetic form of exendin-4), approved for use in the U.S. in 2005, is a 39-amino-acid peptide incretin mimetic that exhibits glucoregulatory activities similar to the mammalian incretin hormone

glucagon-like peptide 1. These actions include glucose-dependent enhancement of insulin secretion, suppression of inappropriately high glucagon secretion, and slowing of gastric emptying (89). People with type 2 diabetes often lose the ability to produce large amounts of insulin in response to the glucose bolus that is released from the gut into the bloodstream following a meal. This results in very high post-prandial blood glucose levels. Exenatide stimulates insulin production in the pancreas in response to post-meal elevations in blood glucose. As insulin is released and blood glucose levels subsequently fall, exenatide allows reduced pancreatic insulin secretion, mimicking the insulin dynamics in patients without diabetes.

Exenatide is injected subcutaneously in a dose of 5 or 10 μ g twice daily, given within 1 h before meals. It can be added to metformin or sulfonylurea or both for patients with less than optimal glycemic control. Side-effects include hypoglycemia when added to sulfonylureas. The most common adverse event is nausea.

In a long-term study, exenatide treatment elicited dose-dependent reductions in body weight (3% at the 10- μ g dose) that did not appear to fully plateau by week 30 (33). Hemoglobin A_{1c} values were reduced by an average of 0.8% at a dose of 10 μ g. In another study comparing exenatide and insulin glargine in type 2 diabetic subjects, both treatments resulted in an average decrease in hemoglobin A_{1c} of 1.1% (73). Exenatide was associated with weight reduction of 2.3 kg, whereas insulin glargine was associated with a weight gain of 1.8 kg over the 6-month study period.

Diabetes and oral/periodontal health

Influence of diabetes on oral health

The impact of diabetes mellitus on the oral cavity has been well researched, and will be reviewed only briefly. A large body of evidence demonstrates that diabetes is a risk factor for gingivitis and periodontitis (98, 109). The degree of glycemic control is an important variable in the relationship between diabetes and periodontal diseases, with a higher prevalence and severity of gingival inflammation and periodontal destruction being seen in those with poor control (16, 48, 68, 77, 127, 135). Large epidemiological studies have shown that diabetes increases the risk of alveolar bone loss and attachment loss

approximately three-fold when compared to nondiabetic individuals (43, 129). These findings have been confirmed in meta-analyses of studies in various diabetic populations (109). In longitudinal analyses, diabetes increases the risk of progressive bone loss and attachment loss over time (134). The degree of glycemic control is likely to be a major factor in determining risk. For example, in a large epidemiological study in the U.S. (NHANES III), adults with poorly controlled diabetes had a 2.9-fold increased risk of having periodontitis compared to nondiabetic subjects; conversely, subjects with well-controlled diabetes had no significant increase in the risk for periodontitis (137). Similarly, poorly controlled type 2 diabetic subjects had an 11-fold increase in the risk for alveolar bone loss over a 2-year period compared to nondiabetic control subjects (134). On the other hand, well-controlled type 2 patients had no significant increase in risk for longitudinal bone loss compared to nondiabetic controls.

Many of the mechanisms by which diabetes influences the periodontium are similar to the pathophysiology of the classic microvascular and macrovascular diabetic complications. There are few differences in the subgingival microbiota between diabetic and nondiabetic patients with periodontitis (119, 150). This suggests that alterations in the host immunoinflammatory response to potential pathogens may play a predominant role. Diabetes may result in impairment of neutrophil adherence, chemotaxis, and phagocytosis, which may facilitate bacterial persistence in the periodontal pocket and significantly increase periodontal destruction (96, 97). While neutrophils are often hypofunctional in diabetes, these patients may have a hyper-responsive monocyte/macrophage phenotype, resulting in significantly increased production of pro-inflammatory cytokines and mediators (115, 116). This hyper-inflammatory response results in elevated levels of pro-inflammatory cytokines in the gingival crevice fluid. Gingival crevice fluid is a serum transudate, thus, elevated serum levels of inflammatory mediators may be reflected in similarly elevated levels of these mediators in gingival crevice fluid. The level of cytokines in the gingival crevice fluid has been related to the level of glycemic control in diabetic patients. In one study of diabetic subjects with periodontitis, those with hemoglobin A_{1c} levels >8% had gingival crevice fluid levels of interleukin-1 β almost twice as high as subjects whose hemoglobin A_{1c} levels were <8% (44). The net effect of these host defense alterations in diabetes is an increase in periodontal inflammation, attachment loss, and bone loss. Ele-

vated pro-inflammatory cytokines in the periodontal environment may play a role in the increased periodontal destruction seen in many people with diabetes.

Formation of advanced glycation end-products, a critical link in many diabetic complications, also occurs in the periodontium, and their deleterious effects on other organ systems may be reflected in periodontal tissues as well (124). Likewise, a 50% increase in messenger RNA for the receptor of advanced glycation end-products was recently identified in the gingival tissues of type 2 diabetic subjects compared to nondiabetic controls (79). Matrix metalloproteinases are critical components of tissue homeostasis and wound healing, and are produced by all of the major cell types in the periodontium (114). Production of matrix metalloproteinases such as collagenase increases in many diabetic patients, resulting in altered collagen homeostasis and wound healing within the periodontium.

Influence of periodontal infection on diabetes

Periodontal diseases are inflammatory in nature; as such, they may alter glycemic control in a similar manner to obesity, another inflammatory condition. Studies have shown that diabetic patients with periodontal infection have a greater risk of worsening glycemic control over time compared to diabetic subjects without periodontitis (133). Because cardiovascular diseases are so widely prevalent in people with diabetes, and because studies suggest that periodontal disease may be a significant risk factor for myocardial infarction and stroke, a recent longitudinal trial examined the effect of periodontal disease on mortality from multiple causes in over 600 subjects with type 2 diabetes (118). In subjects with severe periodontitis, the death rate from ischemic heart disease was 2.3 times higher than the rate in subjects with no periodontitis or only slight disease, after accounting for other known risk factors. The death rate from diabetic nephropathy was 8.5 times higher in those with severe periodontitis. The overall mortality rate from cardio-renal disease was 3.5-fold higher in subjects with severe periodontitis, suggesting that the presence of periodontal disease poses a risk for cardiovascular and renal mortality in people with diabetes.

Periodontal intervention trials suggest a significant potential metabolic benefit of periodontal therapy in people with diabetes. Several studies of diabetic subjects with periodontitis have shown improvements in

glycemic control following scaling and root planing combined with adjunctive systemic doxycycline therapy (65, 66, 101). The magnitude of change is often about 0.9–1.0% in the hemoglobin A_{1c} test. There are some studies in which periodontal treatment was associated with improved periodontal health, but minimal impact was seen on glycemic control (2, 20). Most of these studies used scaling and root planing alone, without adjunctive antibiotic therapy. Conversely, a recent study of well-controlled type 2 diabetic patients who had only gingivitis or mild, localized periodontitis examined the effects of scaling and localized root planing without systemic antibiotics (83). A diabetic control group with a similar level of periodontal disease received no treatment. Following therapy, the treated subjects had a 50% reduction in the prevalence of gingival bleeding and a reduction in mean hemoglobin A_{1c} from 7.3% to 6.5%. The control group, which received no periodontal treatment, had no change in gingival bleeding, as expected, and no improvement in hemoglobin A_{1c}. These results suggest that changes in the level of gingival inflammation after periodontal treatment may be reflected by changes in glycemic control.

Several mechanisms may explain the impact of periodontal infection on glycemic control. As discussed above, systemic inflammation plays a major role in insulin sensitivity and glucose dynamics. Evidence suggests that periodontal diseases can induce or perpetuate an elevated systemic chronic inflammatory state, as reflected in increased serum C-reactive protein, interleukin-6, and fibrinogen levels seen in many people with periodontitis (24, 94). Inflammation induces insulin resistance, and such resistance often accompanies systemic infections. Acute nonperiodontal bacterial and viral infections have been shown to increase insulin resistance and aggravate glycemic control (117, 149). Periodontal infection may similarly elevate the systemic inflammatory state and exacerbate insulin resistance. Tumor necrosis factor- α , produced in abundance by adipocytes, increases insulin resistance by preventing autophosphorylation of the insulin receptor and inhibiting second messenger signaling via inhibition of the enzyme tyrosine kinase (50). Interleukin-6 is important in stimulating tumor necrosis factor- α production; thus, elevated interleukin-6 production in obesity results in higher circulating levels of both interleukin-6 and tumor necrosis factor- α . Periodontal infection can induce elevated serum interleukin-6 and tumor necrosis factor- α levels, and may play a similar role as obesity in inducing or exacerbating insulin resistance.

Conclusions

Diabetic patients are commonly encountered in the dental office. Proper patient management requires close interaction between the dentist and physician. Dentists and other oral health care providers should understand the diagnostic and therapeutic methodologies used in diabetes care. They must be comfortable with the parameters of glycemia that are used to establish a diagnosis and an assessment of patients' ongoing glycemic control. A thorough understanding of the pharmacological agents commonly encountered in this patient population is a must. The dentist should know how these agents can affect the risk for hypoglycemia, and should be able to manage such events should they occur in the office. Dentists must educate patients and their physicians about the interrelationships between periodontal health and glycemic control, with an emphasis on the inflammatory nature of periodontal diseases and the potential systemic effects of periodontal infection. Working with diabetic patients can be challenging and rewarding when open lines of communication are established and thorough patient education is attained.

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