

# Diabetes mellitus

## Considerations for dentistry

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**D**iabetes mellitus (DM) is a metabolic disorder characterized by impaired action, secretion of insulin or both, resulting in hyperglycemia. An estimated 20.8 million people in the United States (7 percent) have DM, and 1.5 million new cases were diagnosed in 2005.<sup>1</sup> Although the definition, the pathophysiological basis and much of management of DM is glucocentric, it is a true metabolic disorder, and a number of metabolic disturbances have been characterized.<sup>2,3</sup> In addition to experiencing well-known complications associated with DM such as premature cardiovascular disease, renal disease, retinopathy and neuropathy, about one-third of people with DM have severe periodontal disease. Attenuated immunity, which occurs as a result of hyperglycemia, and a variety of host factors associated with DM may be the pathophysiological basis for the increased prevalence and severity of periodontal disease.<sup>4</sup> In addition to altering the course of periodontal disease, the diabetic state influences treatment decisions. Osteoporosis increasingly is being associated with DM, which may affect the treatment of periodontal disease because of the involvement of mandib-

### ABSTRACT

**Background.** The connection between oral health and systemic health is bidirectional; systemic illnesses, especially metabolic disorders, affect oral health, and it appears that oral health may affect systemic health.

**Methods.** In this review, the authors outline the basic principles behind diabetes mellitus (DM) and provide some tips to help dentists manage the care of patients with DM better in general practice.

**Results.** DM negatively affects all microvasculature beds, and the soft tissues and bones supporting the teeth are susceptible. There is also strong evidence that the presence of periodontal disease is associated with increased cardiovascular morbidity in patients with DM.

**Conclusions.** DM is a chronic, systemic metabolic disorder in which the orosystemic connection is becoming more understood.

**Clinical Implications.** DM is a relatively common condition and, thus, is one that practicing dentists may encounter frequently.

**Key Words.** Diabetes; insulin; hypoglycemia; periodontal disease.

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ular and maxillary bones.<sup>5,6</sup> Periodontal disease seems to be associated with atherosclerotic cardiovascular disease,<sup>7-9</sup> and having periodontal disease and DM increases cardiovascular disease risk. Physicians and dentists need to be aware of the relationship between DM and periodontal disease and take adequate steps to minimize negative outcomes in patients with DM.

In this review, we provide practicing dentists with an update on the principles of DM, as well as its complications and treatment. Although several types of DM have been described, a number of them are rare, so we mention them only briefly. Our review focuses on providing current information about type 1 DM (absolute insulin deficiency), type 2 DM (obligatory insulin action resistance) and gestational DM (GDM) (typically transient DM lasting during pregnancy).

### CLASSIFICATION AND PATHOGENESIS OF DIABETES MELLITUS

Classification of DM is based on pathogenic processes that can lead to absolute or relative deficiency of insulin resulting in hyperglycemia (Table 1).<sup>10</sup> Eighty-five to 90 percent of patients with DM have type 2 DM, and 5 to 10 percent have type 1 DM. As a good first approximation, patients with type 1 DM initially develop it when they are young, most receive a diagnosis before the end of their teenage years (hence, type 1 DM's being referred to as juvenile diabetes), and they typically are lean. Type 2 DM is considered an adult disorder (as it usually develops in patients older than 40 years), and it frequently is associated with overweight or obese phenotypes. All of these distinctions, however, are becoming blurred, as some young, overweight children receive a diagnosis of type 2 DM and some older, thinner adults have absolute insulin requirements and receive a diagnosis of type 1 DM.

The symptoms that are common for type 1 and type 2 DM include new-onset polyuria and nocturia, accompanying thirst and polydipsia, unexplained weight loss, blurred vision and tiredness. These symptoms are a direct result of high, persistent and fluctuating blood glucose levels. Since there is an absolute deficiency of insulin in type 1 DM, the disorder's presentation typically is acute (less than one week) and accompanied by serious symptoms and signs related to acid-base alterations, whereas many patients with type 2 DM can be relatively asymptomatic for years. It has been estimated that many patients with type 2

DM may have the disorder at least 10 years before it is diagnosed clinically.<sup>11</sup> This idea is supported, in part, by data showing that diabetic complications, which generally take 10 years to develop, can occur in as many as 30 percent of patients who receive diagnoses. With an increase in screening, type 2 DM is being diagnosed in more patients who are asymptomatic.<sup>10</sup>

**Type 1 DM.** There is an absolute insulin deficiency in type 1 DM, with autoimmune destruction of pancreatic beta cells being the most common cause, although any loss of pancreatic tissue can result in insulin dependence (such as pancreatitis, surgical removal or gland destruction from cystic fibrosis). Insulin administration is essential in a typical patient with type 1 DM. If patients do not receive insulin, they develop dehydration resulting from severe hyperglycemia and ketoacidosis, both of which when not treated can lead to coma and death rapidly.

Similar to other autoimmune diseases, type 1 DM has a strong genetic predisposition and a few susceptible genes that are involved primarily in immune function.<sup>12</sup> Although the general population prevalence of type 1 DM is approximately 0.3 percent, it is higher among the first-degree relatives of patients with type 1 DM. The prevalence among the offspring of patients with DM is 3.0 percent if the mother is affected and 6.0 percent if the father is affected. Monozygotic twins have a concordance rate of 30 to 50 percent, and dizygotic twins have a concordance rate of 6 to 10 percent. Variations at the human leukocyte antigen locus account for 40 to 60 percent of genetic susceptibility, with some alleles increasing the risk and some being protective.<sup>13</sup> Patients with type 1 DM are especially susceptible to microvascular complications such as neuropathy, retinopathy and nephropathy, and although coronary artery disease and atherosclerosis can occur, they are less common complications.

**Type 2 DM.** Insulin resistance frequently precedes type 2 DM,<sup>14,15</sup> and it is characterized by a decreased response of the target tissues to the normal levels of circulating insulin. These target

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**ABBREVIATION KEY.** **DM:** Diabetes mellitus. **GDM:** Gestational diabetes mellitus. **HbA<sub>1c</sub>:** Glycosylated hemoglobin. **MI:** Myocardial infarction. **MODY:** Maturity-onset diabetes of the young. **NPH:** Neutral protamine Hagedorn. **OHA:** Oral hypoglycemic agent.

**TABLE 1**

## Abbreviated classification of DM\* based on pathophysiology.

TYPE	ETIOLOGY
<b>Type 1 DM</b>	Autoimmune destruction of beta cells in pancreas, leading to absolute insulin deficiency
<b>Type 2 DM</b>	Constitutional insulin resistance with relative insulin deficiency
<b>Gestational DM</b>	Secondary to insulin resistance (associated with placental hormones) and relative insulin deficiency during second one-half of the pregnancy
<b>Monogenic DM</b>	Extremely rare  Specific gene defects in beta-cell function—for example, MODY <sup>†</sup> 1, MODY 2  Genetic defects in insulin action—for example, Type A insulin resistance
<b>Diseases of Exocrine Pancreas</b>	Usually associated with exocrine pancreatic dysfunction  Pancreatitis/pancreatic neoplasms  Pancreatectomy  Cystic fibrosis, hemochromatosis
<b>Endocrinopathies</b>	Caused by excessive secretion of hormones that counteract insulin, thus creating relative insulin deficiency  Hyperthyroidism  Cushing syndrome  Acromegaly  Pheochromocytoma
<b>Drug- or Chemical-Induced DM</b>	By a variety of actions, some chemicals and drugs increase the susceptibility to DM or unmask it  Glucocorticoids  Nicotinic acid (niacin)  Thiazide diuretics  Diazoxide  β-Adrenergic agonists
<b>Infections</b>	Cytomegalovirus  Rubella
<b>Associated With Other Genetic Syndromes</b>	Down syndrome  Klinefelter syndrome  Turner syndrome
<b>Rare Immune-Mediated DM</b>	Stiff man syndrome  Anti-insulin receptor antibodies
* DM: Diabetes mellitus. † MODY: Maturity-onset diabetes of the young.	

state of hyperinsulinemia. The mechanistic basis for insulin resistance has not been fully characterized, and multiple levels of defects may conspire to cause insulin resistance.<sup>16-18</sup>

In the prediabetic phase, the pancreas is able to secrete increasing amounts of insulin to maintain almost normoglycemia, as well as relatively normal fatty acid levels to overcome the insulin resistance. However, once the beta cells fail to keep up, glucose and fatty acid levels increase and persist, meeting the diagnostic criteria for type 2 DM. For type 2 DM to develop, it is necessary to have a defect in both the action and the secretion of insulin. The progressive disruption of this metabolic pathway is demonstrated in people at all stages of it, and the level at which one diagnoses DM is arbitrary and based on guidelines published by expert panels such as the American Diabetes Association.<sup>10</sup> Emphasis is placed on patients with prediabetes or impaired glucose tolerance who manifest blood glucose levels above the normal range but below the range of frank DM, whether this finding is based on the results of a fasting plasma glucose test (100-125 milligrams per deciliter) or of an oral glucose tolerance test (140-199 mg/dL). As much as 10 to

tissues require higher-than-normal levels of insulin for an adequate response (for example, glucose uptake in muscles or suppression of fatty acid release in fat) to occur, thereby creating a

15 percent of the U.S. population has prediabetes.

Genetic predisposition for type 2 DM is even stronger than for type 1 DM.<sup>19,20</sup> Almost 40 percent of patients who have type 2 DM have at least

one parent who has the disorder. The lifetime risk for a first-degree relative of a patient who has type 2 DM is five to 10 times higher than that of age- and weight-matched patients without a family history of DM. Among monozygotic twin pairs with one affected twin, type 2 DM eventually develops in 60 to 90 percent of initially unaffected twins. Certain racial and ethnic groups are at high risk, including African-Americans, Hispanic Americans, Native Americans, Asian Americans and Pacific Islanders.

**GDM.** GDM is characterized by glucose intolerance that is first diagnosed during pregnancy in a woman who has not had DM.<sup>21</sup> True GDM resolves during the postpartum period. However, as many as 50 percent of women who had GDM remain at risk of developing type 2 DM, so GDM is thought to be a harbinger of DM in later life.<sup>22,23</sup> The pathophysiology of GDM is identical to that of type 2 DM with pancreatic beta-cell dysfunction that is unable to meet the increased demands associated with insulin resistance during pregnancy. A minority of patients may develop type 1 DM for the first time during pregnancy, which emphasizes the connection between pregnancy and autoimmune disease.<sup>23</sup> Recognition of GDM is important because it provides an opportunity to initiate interventional strategies to prevent the development of type 2 DM and to prevent fetal abnormalities by helping the patient maintain tight glycemic control during pregnancy.<sup>24</sup>

## DIAGNOSIS

The American Diabetes Association criteria for the diagnosis of DM are listed in Table 2.<sup>10</sup> Type 1 DM usually is diagnosed after acute onset of symptoms that become metabolically unstable and require immediate evaluation and treatment. However, type 2 DM can differ in manifestation. In prediabetes, a stage during which impaired fasting glucose or impaired glucose tolerance may occur without fulfilling the criteria for type 2 DM, making lifestyle modifications (exercise, weight loss and diet) has been shown to significantly

**TABLE 2**

Diagnostic criteria* for diabetes mellitus.		
TEST CRITERIA	PREDIABETES	OVERT DIABETES MELLITUS
<b>Fasting† Plasma Glucose Test (Milligrams per Deciliter)</b>	≥ 100	≥ 126
<b>Plasma Glucose After 75 Grams Oral Glucose Tolerance Test‡ (mg/dL)</b>	140-199	2 hours: ≥ 200
<b>Random Plasma Glucose Test§ With Symptoms of Hyperglycemia¶ (mg/dL)</b>	Not applicable	≥ 200
* Modified with permission from the American Diabetes Association. <sup>10</sup> Copyright 2008 American Diabetes Association. † Fasting indicates no caloric intake for eight hours prior. ‡ Oral glucose tolerance test involves measurement of plasma glucose at two hours after consuming 75 grams of glucose dissolved in water (this is the typical interval used for diagnosis of type 2 diabetes mellitus). § Random plasma glucose test involves measurement of plasma glucose at any time of the day without any temporal association to caloric intake. ¶ Symptoms of hyperglycemia include polyuria, polyphagia, polydipsia and unexplained weight loss.		

delay, if not prevent, type 2 DM, and this makes the identification of this condition important.

Some people who develop type 2 DM can achieve adequate glycemic control with lifestyle changes such as medical nutritional therapy (also known as dietary therapy), with exercise and weight loss or both, whereas others require treatment with oral hypoglycemic agents (OHAs). A subgroup of patients eventually will need to receive insulin for adequate glycemic control and to prevent ketoacidosis, even though their bodies still produce some insulin. Acute complications such as diabetic ketoacidosis or the nonketotic hyperosmolar hyperglycemic syndrome may occur, requiring immediate hospitalization. Chronic hyperglycemia can result in increased susceptibility to infections and impairment of growth in children. In addition to general symptoms and signs that are present in all types of DM, special markers can help in the differential diagnosis of subtypes.

Patients with type 1 DM generally are lean or have normal body weight and may have other coexisting autoimmune diseases such as hypothyroidism or sprue. Serologic markers of autoimmune processes involved in the development of type 1 DM can be detected in the blood early in the course of the disorder and sometimes throughout life. These markers include antglutamic acid decarboxylase antibodies, islet cell antibodies and anti-insulin antibodies.<sup>10</sup> Routinely checking for antibodies, however, is not recommended owing to low sensitivity.

Type 2 DM usually is diagnosed by means of routine laboratory assessments, after clinical



TABLE 3

## Microvascular and macrovascular complications of diabetes mellitus.

COMPLICATION	FEATURES	PREVENTION
<b>Retinopathy</b>	Hemorrhages, exudates, retinal detachment, macular edema	Annual screening for early diagnosis and treatment  Intensive glucose control
<b>Nephropathy</b>	Most common cause of end-stage renal disease in United States  Earliest sign is microalbuminuria	Intensive glucose control
<b>Neuropathy</b>	Either peripheral or autonomic  Peripheral: pain, tingling, numbness and predisposition to foot ulcers  Autonomic: affects cardiovascular, gastrointestinal and genitourinary systems and awareness of hypoglycemia	Examination of feet at every visit to the health care provider  Intensive glucose control
<b>Cardiovascular Disease</b>	Diabetes mellitus is considered a coronary artery disease equivalent  Risk is increased when associated with hypertension, microalbuminuria or retinopathy  Risk of experiencing a silent myocardial infarction	Aggressive control and treatment of hypertension and hyperlipidemia

evaluation and exclusion of common causes of transient hyperglycemia have taken place. Because there is a long preclinical phase during which blood glucose levels are not high enough to cause symptoms but can cause pathological changes in susceptible tissues, as many as 30 percent of patients have complications such as retinopathy, neuropathy and nephropathy at the time of diagnosis.

### COMPLICATIONS OF DIABETES MELLITUS

The characteristic abnormality in DM is the inadequate action of insulin on target tissues, resulting in abnormal carbohydrate, protein and fat metabolism. DM is a true metabolic disorder and, thus, affects every tissue in the body. Insulin's action on each target tissue is unique to that tissue, so the action of insulin in the liver is different than that in muscle or fat. DM is the most common disorder in patients admitted to hospitals for any cause and accounts for more than 30 percent of health care visits to primary care providers, although it affects less than 10 percent of the general population.<sup>25,26</sup> In general, complications in type 1 DM are those that occur as a result of microvascular disease, which is loosely

defined as affecting arterioles and smaller blood vessels (Table 3). In type 2 DM, both microvascular and macrovascular disease contribute to complications, but greater morbidity is ascribed to damage resulting from macrovascular disease. Periodontal disease also is associated with hyperglycemia; the poorer the control of DM is, the greater the risk of developing periodontal disease. Periodontal disease has been proposed as the sixth complication of DM; the other five complications are retinopathy, neuropathy, nephropathy, cardiovascular disease and peripheral vascular disease.<sup>27</sup>

Microvascular disease involves local endothelial dysfunction and tissue

ischemia. It is responsible for retinopathy, a major cause of blindness in the developed world; neuropathy, which is painful and involves the loss of the sensations of pain and touch, with subsequent risk of developing Charcot joints and ulcers as a result of unattended trauma; and nephropathy, which is a major cause of renal failure and dialysis and is implicated in cardiomyopathy.

Macrovascular disease is responsible for atherosclerotic disease that affects all major arteries (particularly the coronary arteries, carotid arteries and lower limb vascular tree) and can lead to myocardial infarctions (MIs), stroke and peripheral vascular disease. Atherosclerotic processes are made worse by the presence of other conventional risk factors, such as smoking, hypertension and dyslipidemia. Although atherosclerotic cardiovascular death may account for less than 20 percent of all causes of death in patients with type 1 DM, more than 80 percent of patients with type 2 DM will die of cardiovascular causes (heart disease and stroke) prematurely.<sup>28</sup> The combination of DM with diffuse arterial tree disease at many different levels poses a major challenge in the management of any tissue ischemia

(for example, chronic foot ulcers and poor wound healing). Silent MI also is a cause of concern for patients with DM.

Although the role of DM and oral complications is reviewed in another article in this supplement,<sup>29</sup> two other DM-related issues need to be highlighted: DM's effect on joint function (articular and nonarticular components) and bone density.<sup>30</sup> Increased stiffness and loss of flexibility (presumably as a result of increased glycation of long-lived proteins in tendons and extracellular matrices<sup>31,32</sup>) are common clinical findings in patients with DM. At the extreme end of this spectrum is diabetic cheiroarthropathy, which involves significant stiffness of these extra-articular tissues, resulting in significant deformity and inflexibility of joints. When asked, many patients with DM report experiencing joint stiffness.<sup>33</sup> Temporomandibular joint dysfunction has not been studied specifically in patients with DM, but since DM is a metabolic disorder, all joints may be susceptible.

## TREATMENT OF DIABETES MELLITUS

Medical nutrition therapy (also known as dietary therapy) and lifestyle modification form the centerpiece of the management of DM, irrespective of modality of therapy chosen. The goals of therapy are to prevent complications of DM. Tight blood glucose control prevents microvascular complications in both type 1 and type 2 DM.<sup>11,34</sup> Although glycemic control may not be as effective in reducing macrovascular complications, aggressive therapies aimed at blood pressure levels, lipid levels and smoking cessation are effective in preventing macrovascular complications.<sup>35</sup>

**Insulin therapy.** Insulin therapy is the mainstay for patients with type 1 DM, and, in most patients, frequent multiple dosing (basal and bolus) plans are common. Continuous insulin delivery via pumps also is a fairly common practice. All of these methods typically involve subcutaneous injection, and a variety of insulin preparations can be used that allow the physician and patient to select the best method on the basis of cost and flexibility. Insulin therapy should mimic the physiological release of insulin, which is characterized by a continuous basal secretion, to prevent fasting hyperglycemia, as well as prandial insulin release to prevent postprandial hyperglycemia. During fasting, long-acting basal insulin, which has a flat profile without a peak, is used, and at mealtime, a bolus injection of fast-acting insulin

is administered to produce a peak coinciding with absorption of ingested carbohydrates.

In the past, insulin was derived from porcine and bovine sources. These sources have been replaced by recombinant human insulin. Many types of insulin have been developed to produce varying levels of onset of action, ranging from rapid-acting (for example, analog insulins such as aspart, lispro and glulisine) to intermediate-acting (for example, neutral protamine Hagedorn, commonly referred to as NPH) to long-acting (for example, glargine and detemir) (Table 4). Insulin pump therapy, also known as continuous subcutaneous insulin infusion, is portable and provides flexibility and the convenience of fewer injections, especially for patients with type 1 DM. The insulin pump consists of an external pump and a needle inserted into the skin that are connected by tubing. The pump has a reservoir, which is filled with rapid- or short-acting insulin for continuous infusion. The pump can be programmed to deliver different basal and bolus rates and allows delivery of sophisticated regimens of insulin that can be customized to each patient's lifestyle. The basis for any successful insulin therapy is the ability of patients to monitor their own blood glucose levels by using glucometers, education that allows patients to adjust their insulin doses, diet and exercise to produce normoglycemia and prevent hypoglycemia. Insulin therapy is associated with the risk of experiencing significant weight gain and developing hypoglycemia.

**Pramlintide.** Since the secretion of amylin from islets in patients with type 1 DM also is defective, amylin injections may help with glucose control. Amylin decreases postprandial glucagon release and delays gastric emptying (similar to actions of incretins), which may help prevent large excursions in glucose after meals. The commercial preparation of amylin is pramlintide, which is approved by the U.S. Food and Drug Administration for treatment of patients with both type 1 and type 2 DM. However, it has to be injected before each meal. For glucose control in patients with type 1 DM, there are no orally active agents.

**OHAs.** These are the first-line agents used to treat patients with type 2 DM, and they either increase pancreatic insulin secretion or improve insulin action (the term "sensitizer" is used to describe them). Although debate continues about the merits of one kind over another, each class of

TABLE 4

Types of insulin and their profiles.		
TYPE OF INSULIN	CHARACTERISTIC	ACTION
<b>Rapid-Acting Insulin</b> Insulin lispro Insulin aspart Insulin glulisine	Analog insulins  Altered amino acid sequence—promoted insulin monomers that are absorbed rapidly  Injected shortly before meals  Minimize hypoglycemia  Used for continuous subcutaneous insulin infusion and conventional subcutaneous injection therapy	Onset of action: 0.25 to 0.50 hour  Peak action: 1 to 2 hours  Duration of action: 4 to 5 hours
<b>Short-Acting Insulin</b> Regular	Soluble human insulin  Injected 30 to 60 minutes before meals for optimal action; failing to do so results in postprandial hyperglycemia  Less convenient than rapid-acting analogs	Onset of action: 0.50 to 1 hour  Peak action: 2 to 4 hours  Duration of action: 6 to 8 hours
<b>Intermediate-Acting Insulin</b> Neutral protamine Hagedorn, commonly referred to as NPH (isophane suspension)	Formed by adding protamine to human insulin  Acts as both basal and bolus insulin because of its peak at 4 to 6 hours  Hypoglycemia is a problem because of these peaks	Onset of action: 2 to 3 hours  Peak action: 4 to 6 hours  Duration of action: 6 to 8 hours
<b>Long-Acting Insulin</b> Glargine Detemir	Insulin analogs  Glargine: Provides consistent level in plasma for a long duration and is peakless  Detemir: Binds to albumin via fatty acid chain, hence slower absorption and consistent levels	Onset of action: 1 to 2 hours  Peak action: none  Duration of action: up to 24 hours for glargine and 14 to 24 hours for detemir

OHA generally is as effective as the other. At first approximation, most OHAs lead to an average 1.0 to 1.2 percent decrease in glycosylated hemoglobin (HbA<sub>1c</sub>).<sup>36</sup>

The major classes of OHAs, their modes of action and adverse effects are shown in Table 5. Insulin secretagogues are those that stimulate insulin secretion from pancreatic beta cells. They are of value only in patients in whom there is some residual pancreatic function. Their advantage is that they mimic physiological insulin secretion. This class of agents includes sulfonylureas and meglitinides, both of which work through sul-

fonylurea receptors on beta cells to release insulin. Insulin sensitizers improve the action of insulin in target tissues (hepatic, skeletal muscle and adipose tissues) in people with insulin resistance. This class of agents includes biguanides (for example, metformin), which principally reduces hepatic gluconeogenesis and improves muscles' uptake of glucose, and thiazolidinediones (for example, pioglitazone and rosiglitazone) that act primarily on adipose and skeletal muscle to improve insulin action.  $\alpha$ -Glucosidase inhibitors (acarbose and miglitol) decrease glucose absorption in the gut.

**Incretins.** The newest group of oral agents used to treat patients with type 2 DM target the incretin pathway. This group includes dipeptidyl peptidase IV inhibitors. These agents prevent the rapid breakdown of two intestinally secreted hormones (glucagon-like peptide-1 and gastric-inhibitory peptide) that are released in response to meals. These hormones increase insulin secretion, decrease glucagon secretion and delay gastric emptying.<sup>37-39</sup> The incretin pathway

is attenuated in patients with type 2 DM,<sup>40</sup> and oral agents that specifically target the enzyme dipeptidyl peptidase IV increase their half-lives in the bloodstream. Naturally occurring incretins in humans have a short half-life and are not useful therapeutically. Exenatide is a synthetic analog of Gila monster incretin (exendin-4), and it targets the glucagon-like peptide-1 receptor. It is an injectable drug, however, and leads to weight loss, unlike insulin, which causes weight gain.<sup>41-44</sup> Of all the approved agents used to treat DM, only two (metformin and exenatide) consistently reduce weight, as well as improve glycemic con-

trol. All other agents tend to lead to weight gain.

These OHAs can be used alone or in combination with one another and with insulin. Regimens should complement each other and not produce the same effects; for example, combining a sulfonylurea with a meglitinide may not be effective because both act on the sulfonylurea receptors to release insulin. On the other hand, either of these can be combined with any of the insulin sensitizers or the incretin therapies. Use of combination therapies is commonplace for the control of DM.

### Transplantation.

Transplantation of the whole pancreas or isolated islet cells is one of the treatment options for patients with type 1 DM. Islet cell transplantation is experimental, whereas whole pancreas transplantation usually is performed in conjunction with renal transplantation. If successful, both forms of transplantation eliminate or reduce the need for intensive insulin therapy, which has been associated with severe hypoglycemia, to attain nearly normal glycemic control.<sup>45</sup> Whole pancreas transplantation can be performed alone, in combination with kidney transplantation or after kidney transplantation, and its success can be limited by organ availability, graft failure and morbidity associated with immunosuppressive therapy and surgical complications.<sup>46</sup> Improvements in surgical techniques and immunosuppressive therapy regimens have helped reduce morbidity and mortality, making this a viable therapeutic alternative for the treatment of DM.<sup>47</sup> The greatest promise of islet cell transplantation is the possibility of immunosuppression-free

transplantation, obviating the high rates of adverse effects resulting from the use of immunosuppressive agents.

### MONITORING THE COURSE OF DIABETES MELLITUS

The goal of therapy is to prevent complications. For both type 1 and type 2 DM, the prevention of microvascular complications is achieved by improving glycemic control. Since macrovascular disease is the major cause of premature death in patients with type 2 DM, aggressive targeting of the risk factors is imperative.

**TABLE 5**

Oral hypoglycemic agent characteristics.		
AGENT	MODE OF ACTION	ADVERSE EFFECT
<b>Insulin Secretagogues</b>		
Sulfonylureas (currently third generation [glipizide, glimepiride, etc.])	Bind to sulfonylurea receptors on the beta cells triggering release of insulin	Hypoglycemia
	Duration of action and daily doses vary by agent	Weight gain
Meglitinides (repaglinide, nateglinide)	Bind to sulfonylurea receptors	Generally none, but possible hypoglycemia
	Short duration of action, quick onset of action, taken 15 minutes before meals to target postprandial hyperglycemia	
<b>Insulin Sensitizers</b>		
Biguanides (metformin)	Decrease hepatic gluconeogenesis and increase peripheral glucose uptake	Diarrhea, abdominal pains
	Contraindicated in renal insufficiency and heart failure	Risk of lactic acidosis
	Promote weight loss and low risk of developing hypoglycemia when used alone	
Thiazolidinediones (rosiglitazone, pioglitazone)	Activate peroxisome proliferator-activated receptor $\gamma$ to affect glucose and lipid metabolism	Weight gain
	Improve peripheral glucose uptake in skeletal muscle and fat	Water retention
	Take as long as 6 to 12 weeks to attain optimal therapeutic effect	May precipitate congestive heart failure in susceptible people
	No significant risk of hypoglycemia	Possible increase in risk of experiencing bone loss
<b><math>\alpha</math>-Glucosidase Inhibitors</b>		
Acarbose Miglitol	Inhibit $\alpha$ -glucosidase in the gut and, thus, prevent breakdown of some complex carbohydrates into simple sugars that then cannot be absorbed	Bloating, diarrhea and flatulence due to action of colonic bacteria on undigested carbohydrates
	Prevent postprandial glucose excursions	



For glycemic control, it is recommended that the HbA<sub>1c</sub> level (monitored every three months) be maintained at less than 7 percent. If daily blood glucose monitoring is performed, fasting blood plasma levels should be less than 120 mg/dL and blood glucose levels two hours postprandial should be less than 150 mg/dL. For every 1 percent HbA<sub>1c</sub> level, there is an associated increase in complication rates for both microvascular and macrovascular disease.<sup>48</sup> In addition, poor glycemic control leads to poor wound healing and increased postoperative complications. Strict glycemic control, especially when combined with intensive insulin therapy, is desirable to prevent long-term complications, but it is associated with immediate danger of extreme low blood glucose levels.<sup>49</sup> Recurrent hypoglycemia can result in blunting of autonomic response,<sup>34,50</sup> and the first symptom could be decreased consciousness without intervening autonomic symptoms.

Macrovascular risk prevention includes achieving a target lipid profile (total cholesterol < 200 mg/dL, high-density lipoprotein cholesterol > 45 mg/dL in men and > 55 mg/dL in women, low-density lipoprotein cholesterol < 100 mg/dL and serum triglycerides < 150 mg/dL), and blood pressure should be less than 130/80 mm Hg (lower if there is evidence of nephropathy). All patients should exercise and aim to attain and maintain ideal body weight (typically a body mass index of < 25). Medical surveillance includes frequent examination of patients' feet to detect vascular and neuropathic changes, at least an annual full eye examination (including the retinas) and screening for early renal changes via random urinary microalbumin screening. A daily aspirin regimen should be followed unless contraindicated (for example, in patients with hypersensitivity or who are receiving warfarin therapy) in all patients with type 2 DM.

#### **MANAGING THE DENTAL CARE OF PATIENTS WITH DIABETES MELLITUS**

Managing the care of patients with DM in the dental office should not pose a significant challenge. Hypoglycemia is the major issue that usually confronts dental practitioners when they are treating patients with DM, especially if patients are asked to fast before undergoing a procedure. Although patients with DM usually recognize hypoglycemia and take action before becoming unconscious, occasionally they may not. Staff members should be trained to recognize and treat

patients who have hypoglycemia. Patients who have DM and exhibit unusual behavior should raise suspicion among staff members, and a glucometer should be used to test their blood glucose levels.

Every dental office should have a protocol for treating hypoglycemia in conscious and unconscious patients (Box). It is prudent to have snack foods or oral glucose gels or tablets available for such emergencies, especially in offices in which a large number of minor surgical procedures are performed. Glucose gels are particularly helpful in treating children or adults who are uncooperative because the glucose begins to be absorbed when it is exposed to a mucosal surface. Patients taking insulin are advised to carry their own glucometers with them, so asking them to check their own blood glucose levels can be a simple remedy. Patients who are at risk of developing hypoglycemia are those who have received insulin therapy for a while, and screening for patients who report taking insulin should alert staff members to this. Although patients who take OHAs are at a lower risk of developing hypoglycemia than are those receiving insulin, the risk is increased when the patient has renal or hepatic disease. Patients with DM who are diaphoretic should have their blood glucose checked. For any procedure that requires sedation or systemic anesthesia in the outpatient setting, blood glucose levels should be monitored before the procedure and at hourly intervals if surgery is prolonged.

Although no level of hyperglycemia is completely safe, there are no specific guidelines regarding high blood glucose levels and how they should be managed before or during a procedure. If blood glucose levels are elevated to the point that the patient has altered sensorium, it is prudent to avoid performing any procedures in that patient. Having well-controlled blood glucose levels is important for infection prevention and proper healing; however, a scheduled procedure probably does not need to be postponed as long as the patient is conscious and able to follow instructions. Postoperative instructions should emphasize the importance of blood glucose level control during the healing phase, and the patient's primary care physician should be kept informed to help the patient maintain adequate glycemic control.

Loss of pain associated with DM typically affects the distal extremities; central pain sensation is preserved. Joint flexibility is impaired in patients with

DM, and any procedure that may lead to relatively prolonged immobility may require allowing breaks for the patient to move his or her stiff joints. There are no published data to suggest that temporomandibular joint dysfunction is more common in patients with DM, but this possibility may warrant study.

The association of osteoporosis with type 1 DM is well-established, and dental practitioners may need to pay extra attention when procedures involving the bones are considered.<sup>51</sup> For patients with type 2 DM, this relationship is unclear. Although, in general, bone density seems to be preserved, there is an increased risk of experiencing fracture that has been attributed to falls due to hypoglycemia.<sup>5,30,51</sup>

In addition to responding to challenges posed by treating periodontal disease in a patient with DM, dentists can be proactive and play a role in the preventive aspects of DM. They can aggressively screen and diagnose periodontal disease in patients who have DM. They also can assess their general patient populations for those at high risk of developing DM by using, for example, the American Diabetes Association diabetes risk calculator as part of the dental and medical history.<sup>52</sup> The use of this test might result in the detection of people who are at risk of developing DM and possibly some who have undiagnosed DM.

## CONCLUSIONS

Long-term assessment and management of oral health care may reflect the management of DM in general, and assessment of DM control may allow the dental care team to predict the success of oral health care.<sup>53</sup> Using a health care questionnaire, practitioners can ask patients with DM how often they check their blood glucose levels, if they can recall their last HbA<sub>1c</sub> level, if they can report when they last saw their health care provider for DM and when they had their last eye examination. The answers can give practi-

## BOX

### Identification and treatment of hypoglycemia in the dental office.

#### SYMPTOMS OF HYPOGLYCEMIA

Shakiness  
Anxiety  
Palpitations  
Increased sweating  
Hunger

#### SIGNS OF HYPOGLYCEMIA

Tremors  
Tachycardia  
Altered consciousness (lethargy and obtundation or personality change)  
Blood glucose level of less than 60 milligrams per deciliter

#### GENERAL PRINCIPLES

Treatment should be initiated as soon as possible, and staff members should not wait for laboratory results or for a response from a physician.

If the blood glucose levels are extremely low (for example, more than 40 mg/dL), blood should be drawn and sent to the laboratory for accurate blood glucose level measurement because the precision of glucometers is low at extremely low blood glucose levels.

#### CONSCIOUS HYPOGLYCEMIC PATIENT

Treat with 15 grams of simple carbohydrates:

- one-half can of regular soda;
- 4 ounces of regular fruit juice;
- 3 to 4 glucose tablets.

Repeat finger-stick glucose test in 15 minutes.

If the blood glucose level is more than 60 mg/dL, the patient should be asked to eat a meal if it is close to mealtime. If it is not close to mealtime, a mixed snack that includes carbohydrates, proteins and fat (for example, peanut butter and jelly sandwich or graham crackers with peanut butter or milk and crackers) should be given to maintain the patient's blood glucose level. A pure carbohydrate snack will cause the patient to revert back to hypoglycemia quickly. Proteins and carbohydrates in the snack provide sustained glucose release.

If the blood glucose level then is less than 60 mg/dL, repeat treatment of 15 g of simple carbohydrates and check the blood glucose level in 15 minutes. Continue this protocol until the blood glucose level is higher than 60 mg/dL and then follow with a mixed snack.

Ask the patient to discuss the hypoglycemia with his or her physician who is managing his or her diabetes mellitus.

#### UNCONSCIOUS HYPOGLYCEMIC PATIENT OR PATIENT UNABLE TO CONSUME ORAL CARBOHYDRATE

##### With Intravenous Access

Administer 5 to 25 g of 50 percent dextrose immediately; it will be followed by quick recovery.

Notify patient's physician immediately.

##### Without Intravenous Access

Apply glucose gel inside the mouth in a semiobtund patient or treat with 1 mg of glucagon intramuscularly or subcutaneously; the patient should regain consciousness in 15 to 20 minutes.

Repeat the blood glucose test in 15 minutes.

Establish intravenous access and notify the patient's physician immediately.

tioners an idea of how motivated and committed patients are and how well-controlled their DM is. An oral examination also may reflect this. ■

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