

Update on diabetes diagnosis and management

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While dental patients routinely complete a medical questionnaire and have an oral interview during their initial visit, many will be unaware that they have diabetes. Their medical history may not reveal anything suspect. Yet, while talking about general well-being, a patient may mention the classic signs

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and symptoms of diabetes—that is, the triad of polydipsia, polyuria and polyphagia, as well as weakness and fatigue. When this is noted, the patient should be referred to a physician for immediate evaluation. Given the large number of undiagnosed cases of diabetes in the United States (approximately 6 to 7 million), dentists are in a position to offer an enormous public service in making such referrals. Patients with undiagnosed diabetes have a high risk of developing life-threatening systemic complications because they have not yet received treatment. Unrecognized diabetes also can adversely affect their dental treatment. Recognizing the covert signs of uncontrolled glucose levels—poor healing and infection (for example, candidiasis, gingivitis and periodontitis

with significant bone destruction)—and correctly correlating them to the classic signs and symptoms of uncontrolled diabetes can lead to an early diagnosis and prompt treatment.

This article provides an update on the diagnosis and management of diabetes.

Background. The American Diabetes Association has established recommendations for the testing of undiagnosed people. Once diagnosed, those with diabetes must strive to maintain a level of glucose control that results in a metabolism that



approaches that of people without diabetes. The dentist also can provide risk-reduction strategies for people prone to develop diabetes, and refer patients with signs and symptoms suggestive of diabetes to physicians.

Methods. The authors describe criteria for establishing a diagnosis of diabetes and for identifying people at high risk of developing the disease. A combination of approaches in the medical management of type 1 and type 2 diabetes mellitus is presented, along with target outcomes.

Results. Patients with diabetes maintain a glycosylated hemoglobin value of no higher than 7 percent. New therapeutic research includes early clinical trials of islet cell transplantation and therapeutic cloning from human stem cells, which may provide an alternate source of insulin-producing islet cells and, thus, may offer a potential cure for diabetes.

Conclusions. Rigorous metabolic control of diabetes can be achieved through a combination of therapeutic modalities and the establishment and maintenance of target outcomes. The dentist can implement preventive strategies and refer patients with signs and symptoms suggestive of diabetes to physicians.

Clinical Implications. The dentist and physician must work together as a team to achieve rigorous metabolic control of diabetes in their patients.

DIAGNOSIS OF DIABETES

The American Diabetes Association¹ has established criteria for testing undiagnosed people. They suggest that all people aged 45 years and older, especially those with a body mass index greater than or equal to 25 kilo-

grams/square meter, should have a fasting plasma glucose, or FPG, obtained. An FPG greater than 126 milligrams/deciliter is diagnostic for diabetes. If the FPG is 110 to 126 mg/dL, then an oral glucose tolerance test, or OGTT, should be performed to determine the degree of glucose intolerance. If the FPG score is less than 110 mg/dL, the test should be repeated at three-year intervals. While an FPG of more than 126 mg/dL is the preferred diagnostic test owing to its ease of administration and lower cost, a random plasma glucose level of greater than 200 mg/dL in the presence of the classic symptoms also is acceptable. In each instance, positive findings must be confirmed by repeat testing on a subsequent day. Neither the glycosylated hemoglobin, or HbA_{1c}, nor the OGTT measurements are currently recommended for initial diagnostic use because of their lack of reproducibility. Testing should be considered at a younger age and carried out more frequently in people who are at high risk (Box). While the American Diabetes Association does not specify the age at which to begin this screening, the American Association of Clinical Endocrinologists, or AACE, suggests that it should be initiated at the age of 25 years.²

ESTABLISHING TARGET OUTCOMES

While the management of the patient with diabetes should be determined individually, based on the patient's clinical status and willingness to actively participate in self-care, there are recommended goals. These goals are designed to achieve near-normal metabolic control, prevent or delay microvascular and macrovascular complications, and allow a high quality of life. Published large-scale studies have confirmed the importance of tight control for both type 1 and type 2 diabetes.³⁻⁵ There is a direct and significant reduction in the incidence and progression of

BOX

RISK FACTORS IN THE DEVELOPMENT OF DIABETES.

- Obesity (a weight higher than 120 percent of ideal body weight or a body mass index higher than 27 kilograms per square meter)
- High-risk ethnic background (African-American, Hispanic, American Indian, Asian, Pacific Islander)
- Hypertension
- High-density lipoprotein level lower than 35 milligrams per deciliter or a triglyceride level higher than 250 mg/dL
- A first-degree relative with diabetes
- History of gestational diabetes or delivery of a baby weighing more than 9 pounds
- Impaired glucose tolerance or impaired fasting glycemia (history of blood sugar level between 110 and 126 mg/dL)
- History of vascular disease or polycystic ovarian disease

both microvascular and macrovascular complications with lowered HbA_{1c}. This test provides a measure of the patient's average glycemia over the preceding two to three months and is an excellent tool for monitoring patient outcomes⁶ (Table 1).

Because the available data have failed to identify the optimum level of control for particular patients, consensus regarding the target HbA_{1c} is lacking. The American Diabetes Association recommends an HbA_{1c} of 7 percent, while the AACE recommends that a value of 6.5 percent is a reasonable goal, but targets 6.0 percent as the optimal endpoint.^{1,6} Since the HbA_{1c} only repre-

TABLE 1

CORRELATION BETWEEN GLYCOSYLATED HEMOGLOBIN LEVEL AND MEAN PLASMA GLUCOSE LEVELS.

GLYCOSYLATED HEMOGLOBIN (%)	MEAN PLASMA GLUCOSE (mg/dL)*
6	135
7	170
8	205
9	240
10	275
11	310
12	345

* mg/dL: Milligrams per deciliter.

TABLE 2**RECOMMENDATIONS REGARDING PLASMA GLUCOSE, BLOOD PRESSURE AND LIPIDS FOR NONPREGNANT ADULTS WITH DIABETES.**

FACTOR	RECOMMENDED LEVEL
Glycemic Control (Plasma Glucose) Preprandial Peak postprandial	90-130 mg/dL* < 180 mg/dL
Blood Pressure	< 130/80 mm Hg [†]
Lipids Low-density lipoprotein Triglycerides High-density lipoprotein	< 100 mg/dL < 140 mg/dL > 40 mg/dL
* mg/dL: Milligrams per deciliter. † mm Hg: Millimeters of mercury.	

sents the mean glucose level, glycemic control is best judged by the combination of the HbA_{1c} (performed routinely every three months) and the concurrent results of the patient's blood glucose monitoring. Patients can be taught to perform glucose tests at home using glucose meters that require a single drop of blood (obtained from multiple sites including fingertips, forearm, upper arm, thigh, calf and the fleshy part of the hand). These systems are small, simple to use and inexpensive. They are sufficiently accurate to provide immediate feedback, allowing the patient and provider to make informed and timely changes to the regimen. Most people with diabetes have a high frequency of wide fluctuations in blood sugar levels; therefore, it is important to counsel the patient to avoid checking blood glucose at the same time of the day. Instead, glucose monitoring should be done at a variety of times—premeal, postmeal, before and after exercise and at bedtime—to best determine the impact that food, activity and even stress can have on the ambient serum glucose level. The overall goal of diabetes management is to achieve a level of metabolic control that approaches that of a person without diabetes¹ (Table 2).

DIABETES MANAGEMENT

Achieving metabolic targets that approach levels commonly found in people without diabetes requires treatment programs that are designed to reproduce as closely as possible the pattern of glucose and endogenous insulin levels that would have existed if the patient did not have the disease. The patient with type 2 diabetes has two

defects that occur simultaneously: insulin resistance and insulin deficiency. Insulin resistance is a common phenomenon of the patient with type 2 diabetes and it usually antedates the onset of the disease. Insulin resistance prevents the target tissues (especially the muscle and liver) from responding to normal circulating concentrations of insulin. It affects glucose disposal in muscle and fat and reduces insulin suppression of hepatic glucose output. Insulin deficiency develops over time—initially as a loss of first-phase insulin release with a compensatory increase in the second

phase. This hyperinsulinemic response does not persist and the insulin secretory capacity of the beta cell begins to wane. Eventually, the patient becomes increasingly more insulinopenic. Since this is a pathophysiological response, every individual with type 2 diabetes has the potential to require supplemental insulin. The eventual need for insulin therapy should be considered a sign of the disease's progression rather than a failure of the patient. Treatment regimens for patients with type 2 diabetes should address both the insulin resistance and insulin deficiency, and must include both nonpharmacological and pharmacological interventions.

The patient with type 1 diabetes has an absolute insulin deficiency. As a consequence, these patients must receive insulin replacement. Oral hypoglycemic agents do not restore insulin secretion. Nonpharmacological interventions can facilitate control, but they can never substitute for exogenous insulin.

In the patient with type 2 diabetes, initial treatment begins with nonpharmacological interventions, specifically, a healthful meal plan, exercise and, when appropriate, weight loss. The meal plan should be designed to promote overall health through optimal nutrition, to facilitate improved blood glucose and lipid levels, and to provide sufficient calories to achieve or maintain reasonable weight. Interestingly, only a moderate amount of weight loss is needed to improve insulin resistance. Currently, there are three approaches to the diabetic diet: general recommendations that emphasize the U.S. Department of Agriculture's Food Guide Pyramid, calorie-reduced plans using

the exchange list and carbohydrate counting.⁷

Carbohydrate counting is frequently used when the patient is taking insulin, because the patient can precisely match food intake to the insulin therapy. This approach allows for the greatest flexibility in food choices, but to be successful, it requires careful attention to portions.

Exercise enhances insulin sensitivity, improves blood glucose control and aids in weight reduction. It is

important to encourage patients to enroll in structured programs that emphasize lifestyle changes, including education, reduced fat (< 30 percent of daily energy), regular physical activity and regular contact between enrollees (this refers to group classes, peer support groups and even Internet chat rooms). Several studies have demonstrated that structured programs can produce long-term weight loss of 5 to 7 percent of starting weight.⁸ When these measures fail to allow the patient to meet the target HbA_{1c} levels, then oral hypoglycemic agents must be instituted (Table 3).

The best time to initiate therapy with oral hypoglycemic agents and the optimal choice for the starting medication still is being debated.

Three classes of oral hypoglycemic agents are available. Each class reduces plasma glucose levels by one or more methods: increasing insulin secretion, reducing insulin resistance or delaying glucose absorption by the gut. Since insulin resistance is present before the onset of type 2 diabetes, and because the failing beta cell occurs later in the disease, many have argued that the therapy should be initiated with an insulin sensitizer and that the sensitizers should be started before the metabolic control decompensates.^{9,10}

TABLE 3

TYPES AND DOSAGES OF ORAL HYPOGLYCEMIC AGENTS.				
CLASS	DRUG	DOSAGE	DOSES PER DAY	
Insulin Secretagogues* Sulfonylureas	Chlorpropamide	100-500 mg [†]	1	
	Glipizide	5-40 mg	1-2	
	Glyburide	1.5-20 mg	1-2	
	Glimepiride	1-8 mg	1	
	Nonsulfonylureas	Nateglinide	180-360 mg	2-4
	Repaglinide	0.5-16 mg	2-4	
Insulin Sensitizers‡ Biguanides Thiazolidinediones	Metformin	500-2,250 mg	2-3	
	Pioglitazone	15-45 mg	1	
	Rosiglitazone	4-8 mg	1-2	
Agents That Delay Carbohydrate Absorptions§ Alpha-glucosidase inhibitors	Acarbose	25-300 mg	3	
	Miglitol	25-300 mg	3	
Combination Agents	Rosiglitazone and Metformin [‡]	4-8 mg/ 1,000-2,000 mg	2	
	Metformin and Glyburide ^{**}	1.25-10 mg/ 500-2,000 mg	1-2	
	Metformin and Glipizide ^{**‡}	2.5-10 mg/ 500-2,000 mg	1-2	
* Stimulates beta cells. † mg: Milligram(s). ‡ Stimulates glucose uptake by muscle and adipose tissue and reduces the liver's glucose output. § Delays the gut's glucose absorption.				

Metformin, pioglitazone and rosiglitazone are used to improve insulin sensitivity. Metformin improves sensitivity of the liver and reduces hepatic glucose output, while pioglitazone and rosiglitazone improve peripheral glucose uptake at the muscles. Selection should consider the limitations of these drugs. For example, a commonly used insulin sensitizer, metformin, has been associated with intractable lactic acidosis. If a patient has mild kidney disease, or is at risk of developing congestive heart failure, severe infection can significantly increase the risk of lactic acidosis. Communication with the patient's primary physician is warranted to determine if the drug should be withheld.¹¹

Pioglitazone and rosiglitazone are thiazolidiones that activate the peroxisome proliferator-activated receptors, or PPARs.¹² Activation of the PPARs regulates the transcription of insulin-sensitive genes involved in the control of glucose production, transport and utilization, and they participate in the regulation of free fatty acid metabolism. Stimulation of PPAR-gamma and -alpha receptors increases the expression of another molecule called ABCA1 that exports cholesterol from macrophages. Thus, exploiting

TABLE 4

INSULIN PREPARATIONS.					
TYPE OF INSULIN	ACTION	TIME TO ONSET	TIME TO PEAK	DURATION OF ACTION	FORM
Human					
Regular	Short to intermediate	0.5 hour	2-4 hours	6-12 hours	Vial, cartridge, pen
Neutral protamine Hagedorn, or NPH	Intermediate	1.5 hours	4-6 hours	14-16 hours	Vial, cartridge, pen
Lente	Intermediate	3 hours	7-9 hours	14-20 hours	Vial
Ultralente	Intermediate to long-acting	4 hours	8-14 hours	24 hours	Vial
Analogs					
Lispro	Rapid	0.25 hour	1.25 hours	2.5 hours	Vial, cartridge, pen
Insulin Aspart	Rapid	0.25 hour	1.25 hours	2.5 hours	Vial, cartridge, pen
Glargine	Long-acting	2 hours	none	≥ 24 hours	Vial
Insulin Mixtures*					
Humulin 70/30 Novolin 70/30	Human NPH 70%	0.5 hours	4 hours	14-16 hours	Pen, vial
	Human Regular 30%	6.5 hours	4 hours	14-16 hours	
Humulin 50/50	Human NPH 50% Human Regular 50%	0.5 hour	4 hours	14-16 hours	Vial
Humalog 75/25	Human NPH 75% Humalog 25%	0.25 hour	2.5 hours	14-16 hours	Pen, vial
Novolog 70/30	Human NPH 70% Novolog 30%	0.25 hour	2.5 hours	14-20 hours	Penfil cartridge, vial

* Humulin is manufactured by Eli Lilly, Indianapolis, Ind.; Novolin, Novo Nordisk Pharmaceuticals, Princeton, N.J.; Humalog, Eli Lilly; Novolog, Novo Nordisk Pharmaceuticals.

this pathway may be a way to control lipid levels, inflammation and atherosclerosis.

Proponents of using secretagogues as initial therapy suggest that increasing insulin secretion rapidly lowers blood glucose levels, thus reversing the glucose toxicity caused by severe hyperglycemia. With lowered blood glucose levels, the beta cell may be able to resume more normal function. Regardless of the drug class selected, when it is used as monotherapy, a 0.5 to 2 percent reduction in HbA_{1c} can be expected.¹³ When combination therapy is used, either with a secretagogue and sensitizer or with two sensitizers, there is a further glucose reduction, with HbA_{1c} reductions of 0.7 to 1.7 percent.^{14, 15} Many feel that these prefixed dose combinations facilitate patient compliance and have synergistic properties that allow lower dosing.

Type 1 diabetes is caused by autoimmune

destruction of the pancreatic insulin-producing beta cells and results in profound insulin deficiency. As a consequence, these patients must receive insulin replacement. Insulin also is indicated for patients with type 2 diabetes who have persistent hyperglycemia either due to progressive loss of insulin secretion, or acute decompensation due to stress, illness, infection or concurrent medications. Current insulin therapy, however, has not been able to mimic normal physiology. Several problems exist. First, insulin must be injected subcutaneously three or more times per day to mimic the required concentration of insulin both in the preprandial and postprandial state. Second, subcutaneous insulin injections deliver insulin initially to the systemic circulation and only secondarily into the portal circulation. Hence, it is not possible to achieve the normal endogenous portal-to-systemic insulin ratios.

Finally, much of the insulin is injected in a form that is not initially soluble, leading to fluctuations in serum insulin levels, even after injection of the same dosage.^{15,16} Table 4 shows types of insulin preparations and their onset, peak and duration of action.

Recent advances in insulin therapy have been designed to overcome some of these limitations. Insulin algorithms are designed to deliver a near-continuous supply of insulin to match the body's basal requirements and provide larger quantities (bolus) of insulin to ensure adequate glucose uptake at meals. Insulin can be administered using a traditional insulin syringe, an insulin pen or a subcutaneous continuous insulin pump, or SCII.^{17,18} Optimal insulin replacement therapy consists of regimens that provide for the basal and the bolus needs of the individual. In other words, the regimen must be designed using insulins with different action profiles (Table 4). With SCII, only one insulin type is required, either short- or rapid-acting insulin, because the system provides insulin continuously. When the patient wishes to increase the delivery of insulin for a meal or a snack or to react to an undesired glucose level, a button is pushed to activate a bolus of insulin.¹⁹

The purpose of the basal program in the insulin pump is to release insulin continuously and thus maintain glucose homeostasis by preventing significant glycogenolysis from the glycogen stores in the liver.²⁰ If there is disruption in this finely tuned glucose control, then rapid and severe hyperglycemia results, with diabetic ketoacidosis, or DKA. The signs and symptoms of DKA include nausea, disorientation, abdominal cramps and fatigue; these often resemble flulike signs and symptoms. The dentist should recognize signs and symptoms of DKA and call the physician immediately if the glucose meter readings show severe hyperglycemia. The physician may instruct the dentist to administer a bolus of rapidly acting insulin from the patient's backup supplies of insulin and insulin syringes.

In type 1 diabetes, where insulin resistance is usually not a factor, patients will require approximately 0.5 to 1.0 units of insulin/kilogram per 24 hours (most will require 0.6 U/kg).^{15,17} Patients with type 2 diabetes may require from 0.3 to 1.5 U/kg. In both cases, body type (lean patients often require fewer insulin units/kilogram), activity, stress and residual endogenous insulin will deter-

mine the actual insulin requirement. A variety of factors may influence the effectiveness of the insulin therapy. These factors include the injection site, the depth of penetration, the lag time between injection and the meal, the food consumed, activity and stress. To achieve near-normoglycemia, insulin dosages must be altered to compensate for the impact of these variables. Therefore, it is necessary to prescribe more than an exact set of insulin instructions. Patients must be given guidelines for adjusting the insulin dose proactively, as well as guidelines for responding to blood glucose levels that are outside of the target range. Patient self-monitoring of blood glucose levels, accompanied by a program of education, can give the patient the knowledge and skill needed to make these adjustments.

PREVENTION

Reducing the risk factors for developing diabetes may be an important approach in the prevention of this disease, particularly type 2 diabetes. The incidence of type 2 diabetes in children and adolescents is increasing and may be related to dietary obesity. Although there are insufficient data to make general recommendations, a recent American Diabetes Association consensus statement provides guidance regarding the prevention, screening and treatment of type 2 diabetes in young people.²¹ Aside from nonmodifiable risk factors such as age, family history and genetics, a person can change his or her lifestyle to include regular exercise, maintaining a healthful low-fat diet, and visiting a physician and dentist on a regular basis. However, in a recently published survey, people with diabetes were somewhat less likely to visit their dentists for routine examinations and were somewhat more likely to visit for dental care only when treatment was needed (for example, cleanings, restorations and oral surgery).²² Furthermore, in the same survey, adults with diabetes rated their overall oral health somewhat lower than did people without diabetes (control group), and they rated the need to visit a physician as a higher priority than did control subjects.²² Clearly, preventive strategies must be in place for people, particularly those at risk of developing diabetes, and for those with diagnosed disease. The dentist can have a major role, not only in the implementation of preventive strategies in both types of patient populations, but also in modifying oral health perceptions and counterproductive attitudes.

PANCREAS AND ISLET TRANSPLANTATION THERAPY/STEM CELL RESEARCH

Pancreas and islet transplantation are not routine management options. In each case, the patient requires immunosuppressive therapy, which comes with associated risks. In general, pancreas transplantation, a major surgical intervention, is considered only when a patient requires another transplantation—usually a kidney. However, the success rate at one year for simultaneous kidney-pancreas transplantations is at 90 percent.²³ While islet transplantation has the advantage of requiring only minor surgery, allowing the achievement of normal blood sugar values with little surgical risk, there are still major limitations. Until about three years ago, there had been only a few isolated successes with islet cell transplantation and then only for a short period. Recent work has shown consistent success with islet transplantation in one group; patients in the study were infused through the portal vein of the liver with beta cells isolated from human cadaver pancreases.²⁴ Studies are under way to confirm this success in other laboratories; however, it is difficult to obtain and purify islets.

At present, there are only 10,000 pancreases available for transplantation per year.²⁵ Since it currently takes two to three pancreases per transplantation, only approximately 3,000 to 5,000 patients could be treated per year. In addition, the process still requires the use of multiple immunosuppressive agents. The risk of these drugs limits the use of this procedure to people who already have significant morbidity from their diabetes. Methods of developing means of immunotolerance not requiring drug therapy are under way, along with research to find alternative sources of islets.²⁶

The new field of stem cell research has focused on the provision of islet cells as one of its early goals. Human progenitor stem cells are pluripotent and thus capable of differentiating into a number of mature, functional cell types.²⁷ For example, under defined conditions *in vitro*, these stem cells may be induced to differentiate into fully functional, insulin-producing beta cells. These cells could then be infused through the portal vein into a patient who is profoundly insulin-deficient (type 1 diabetes). Insulin-producing cells that previously were lost would be replaceable. Such an approach, known as therapeutic cloning, will represent a significant

advance toward the cure for diabetes mellitus, as well as possibly other chronic debilitating diseases of our time.

GENE THERAPEUTICS

While cell transplantation and stem cell research are approaches that ultimately may provide sources of insulin-producing cells, the promising application of *in vivo* gene transfer may produce therapeutic proteins or hormones.²⁸ Salivary glands are recognized as classic exocrine glands, yet they also may secrete in an endocrine manner (that is, directly into the bloodstream).²⁹ This role has never been proven in humans. However, using gene-transfer techniques with a recombinant adenovirus, Kagami and colleagues³⁰ demonstrated that rat salivary glands, infected with this virus via intraductal retrograde infusion, were able to secrete human alpha₁-antitrypsin directly into the blood stream. By using *in vivo* gene-transfer technology, this study reported that a mammalian salivary gland can secrete in an endocrine as well as in an exocrine manner (that is, directly into the saliva).

Other studies showed a similar result following the infection of rat salivary glands with a recombinant adenovirus encoding human tissue kallikrein, growth hormone and aquaporin-1, or AQP1.³¹⁻³³ AQP1 is the archetypal mammalian water channel, and rats receiving AQP1 after irradiation secreted saliva at control levels; this approach may be useful for patients with salivary hypofunction following head and neck irradiation for cancer, or for those with primary Sjögren's syndrome. These studies lend support to the notion that salivary glands may prove to be a useful target site for transgene delivery³⁴⁻³⁶ and, thus, for the therapeutic correction of some systemic single-protein-deficiency disorders including, potentially, insulin deficiency in diabetes mellitus.

CONCLUSION

The American Diabetes Association has established criteria for testing undiagnosed people, and testing should be done more frequently in people at high risk of developing the disease. The overall goal of diabetes management is to achieve a level of metabolic control that approaches that of the individual without diabetes, using target outcomes. Therapeutic approaches include the use of insulin, oral hypoglycemic agents and weight control. The dentist has an important role in refer-

ring patients with oral manifestations suggestive of diabetes to physicians for evaluation and treatment. The dentist also can recommend preventive, risk-reduction strategies to patients who may be more likely to develop diabetes, and modify counterproductive attitudes toward oral health care in those with diagnosed disease. Islet cell transplantation as a cure for diabetes is in its early clinical trials and a number of challenges remain. Therapeutic cloning may provide an alternate source of insulin-producing cells and thus a cure for diabetes. Gene-transfer techniques using recombinant adenovirus may alternatively provide another site (that is, the salivary gland) for the production and secretion of insulin. These techniques have not yet been applied in human clinical trials, but their potential is exciting. <

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