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INVITED REVIEW

Update on diabetes mellitus: prevention, treatment, and association with oral diseases

M Skamagas, TL Breen, D LeRoith

Division of Endocrinology, Diabetes and Bone Diseases, Mount Sinai School of Medicine, New York, NY, USA

Diabetes mellitus is a prevalent disease that affects millions of people worldwide and has paralleled the growing population of overweight and obese individuals. Early detection of prediabetes and diabetes, as well as lifestyle interventions including diet and exercise, are the overarching objectives in preventing and managing diabetes. For individuals who do not achieve glycemic control with lifestyle modification, there are newer medication classes that assist with weight loss, more physiologic insulins with convenient delivery systems, and old standbys like metformin and thiazolidinediones. Glycemic control along with blood pressure and cholesterol management reduce microvascular and macrovascular disease including cardiovascular events. Mounting evidence demonstrates that diabetes is a risk factor for periodontitis and possibly oral premalignancies and oral cancer. The systemic inflammatory response generated by inflamed periodontal tissue may in turn exacerbate diabetes, worsen cardiovascular outcomes, and increase mortality. Thus, oral medical and surgical physicians are vital in treating oral pathology, recognizing new cases of diabetes, and counseling people with diabetes to promote oral health. This article presents updates in the diagnosis, risk factors, prevention, management, and peri-oral complications of diabetes to assist oral health professionals in providing optimal care to patients with diabetes.
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Introduction

Diabetes is a far reaching epidemic that creates morbidity and mortality for millions of people in both developed and developing countries. According to World Health Organization (WHO) estimates, there were 171 million people in the world with diabetes in the year 2000. Five percent of all deaths throughout the world are attributed to diabetes (Roglic *et al*, 2005), and the epidemic continues to grow with the concurrent rise in obesity and deteriorating lifestyle behaviors. Based on data from the US National Health Interview Survey, the estimated lifetime risk of developing diabetes for a person born in 2000 is a staggering 33% for males and 38.5% for females (Narayan *et al*, 2003). Moreover, diabetes is shortening people's lives; the estimated decrease in life expectancy for a person diagnosed with diabetes at the age of 40 is about 12 years for men and 14 years for women.

The complications of diabetes that contribute to morbidity and mortality include microvascular disease, macrovascular disease, in particular cardiovascular disease, and perioral disease. Severe periodontal disease, which is found in 5–15% of most populations (Petersen, 2003), leads to tooth loss, and extends beyond local disease to produce systemic effects, exacerbating the inflammatory milieu, increasing insulin resistance, and potentially worsening cardiovascular disease. In addition, diabetes increases the risk of oral pathology including acute infections, periodontitis, and possibly premalignant and malignant lesions. Given all of the above, it is imperative that oral health practitioners and endocrinologists aggressively manage the oral health and diabetes of these individuals. Being aware of the latest advances in the diagnosis, prevention, and treatment of diabetes will assist oral health professionals in providing better quality of care for people with diabetes.

Classification of diabetes: type 1, type 2, and secondary causes

Approximately 85–90% of individuals with diabetes have type 2, resulting from a combination of impaired insulin secretion and insulin resistance. The majority of people with type 2 diabetes are asymptomatic in the first several years of the disease during which time microvascular and macrovascular changes begin to accumulate. The initial defect is in the first phase of insulin secretion, leading to overcompensation in the second

Correspondence: Derek LeRoith, MD, PhD, Mount Sinai School of Medicine, One Gustave L Levy Place, Box 1055, New York, NY 10029, USA. Fax: 212 241 4218, E-mail: derek.leroith@mssm.edu
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phase of insulin secretion and hyperinsulinemia. Insulin resistance causes decreased ability of muscle, adipose, and liver to respond to insulin, resulting in decreased glucose uptake by peripheral tissues and increased gluconeogenesis by the liver. Progression of untreated diabetes leads to loss of beta cells in the islets of Langerhans with eventual insulin deficiency (Tataranni and Bogardus, 2004). As a result, many patients who are initially treated with oral medicines will at some point require insulin. The increasing incidence of type 2 diabetes closely parallels the overweight and obesity epidemics. Visceral abdominal fat tissue generates cytokines, called adipokines, which are linked to insulin resistance, diabetes, hypertension, and dyslipidemia. Similar cytokines released by inflamed periodontal tissue, including TNF-α and IL-6, may contribute to worsening of diabetes (Loos *et al*, 2000).

Type 1 diabetes, formerly described as insulin-dependent diabetes or juvenile diabetes, makes up about 5% of diabetes cases, and is a condition of absolute insulin deficiency that results from beta cell destruction. These individuals present in childhood, adolescence, or young adulthood, typically with acute symptomatic hyperglycemia and a hypercatabolic insulinopenic state (polyuria, polydipsia, dehydration, weight loss) or with diabetic ketoacidosis (nausea, vomiting, fatigue, abdominal pain, altered mental status). The overwhelming majority have evidence of automimmunity, with serum antibodies, to glutamic acid decarboxylase, islet cell antibodies or insulin antibodies especially early on in the course of the disease.

Not uncommonly, an individual may not fit the typical characteristics of pure type 1 or type 2 diabetes. Ketoacidosis-prone diabetes, also called Flatbush diabetes, describes individuals with type 2 diabetes, largely of African-American descent, who are more likely to develop diabetic ketoacidosis, a complication usually seen in type 1 diabetes. Latent autoimmune diabetes of adulthood (LADA) is comprised of patients who have evidence of autoimmunity but present with diabetes after the age of 30. Individuals with LADA tend to be leaner adults whose diabetes presented acutely, have a personal or family history of autoimmune disease (Fourlanos *et al*, 2006), respond poorly to oral diabetes medications, and many eventually require insulin. People with type 1 diabetes were traditionally described as lean individuals; however, obese youth are not immune from developing type 1 diabetes. Furthermore, those with type 1 diabetes who become overweight or obese may suffer some degree of insulin resistance, requiring higher doses of insulin and potentially benefiting from similar oral insulin sensitizing drugs used in type 2 diabetes.

The remaining 5–10% of individuals with diabetes have a secondary cause, some of which are inherited and others acquired. In addition, many people with diabetes have superimposed pro-glycemic insults that make glucose control more difficult. The secondary causes and exacerbating factors include: genetic mutations that interfere with beta cell function, formerly called maturity onset diabetes of the young; pancreatic disease including cystic fibrosis, chronic pancreatitis, hemochromatosis, or pancreatic resection; endocrinopathies such as Cushing's syndrome, acromegaly, glucagon- or somatostatin-secreting tumors, and pheochromocytoma; drug-induced diabetes due to corticosteroids, immunosuppressants used in organ transplants including tacrolimus and cyclosporine, atypical anti-psychotics including clozapine and olanzapine, cardiovascular medicines including niacin and beta-blockers, and HIV protease inhibitors; and rare mitochondrial disorders.

Risk factors for diabetes

A multitude of risk factors, some modifiable and others fixed, predispose an individual to type 2 diabetes. Family history of diabetes in first degree members, increasing age, and ethnicity (Hispanic, African-American, Asian-American, Native-American) are classic non-modifiable risk factors. Being overweight with a body mass index >25 kg m^{-2}, sedentary lifestyle, and pre-existing impaired glucose homeostasis are modifiable risk factors. Other factors include gestational diabetes mellitus, prior delivery of a baby weighing >9 lbs, polycystic ovarian syndrome, hypertension, and dyslipidemia (elevated triglycerides or low HDL cholesterol).

Diagnosis

Screening for diabetes is recommended by the American Diabetes Association (ADA) in individuals at risk for diabetes and in all people over the age of 45 (Standards of Medical Care in Diabetes, 2007). A fasting glucose $\geq$126 mg dl^{-1}, or a random glucose or post oral glucose challenge value $\geq$200 mg dl^{-1} meet criteria for diabetes (see Table 1). Fasting glucose is an easy, cheap, and reproducible method of screening a patient. However, fasting glucose will not detect all diabetes; one may proceed to an oral glucose tolerance test (oGTT) in an individual with an impaired fasting glucose (IFG) or in a high risk individual who has a normal fasting glucose. Plasma glucose is measured at baseline and 2 h after ingestion of a 75 g load of glucose. IFG and impaired glucose tolerance (IGT) refer to individuals whose glucose homeostasis is abnormal, but who do not quite qualify as having diabetes.

The diagnosis of diabetes relies on two abnormal glucose values measured on different days. The occa-

Table 1 Diagnosis of diabetes and impaired glucose homeostasis, ADA guidelines

Fasting glucose	Glucose (mg dl^{-1})
Normal	**<100**
Prediabetes: impaired fasting glucose	**100–125**
Diabetes	**≥126**
2 h postglucose challenge (oGTT) or random glucose	
Normal	**<140**
Prediabetes: impaired glucose tolerance	**140–199**
Diabetes	**≥200**

oGTT, oral glucose tolerance test.

sional patient, particularly with type 1 diabetes, will present dramatically with polyuria, polydipsia, weight loss, and plasma glucose greater than 200, immediately qualifying the individual for a diagnosis of diabetes and necessitating insulin treatment. Diabetes is not diagnosed using a Hemoglobin A_{1C} (HbA_{1C}) measurement. However, the HbA_{1C} is a convenient, accurate means of following glycemic control in a patient already diagnosed with diabetes. It represents the amount of hemoglobin that is glycosylated, and estimates average blood glucose over the prior 3 months which is the lifespan of a normal erythrocyte. An HbA_{1C} of six approximates the average blood glucose at 135 mg dl^{-1}, a value of seven at 170 mg dl^{-1}, a value of eight at 205 mg dl^{-1}, etc.

Significance of prediabetes

The prediabetes designations of IFG and IGT are defined by a fasting glucose of 100–125 and a postglucose challenge value of 140–199, respectively. Progression from normal glucose tolerance to impaired glucose homeostasis and finally to diabetes occurs over years. A 'prediabetic' individual does not exist in a silent transition period between 'normal' and the inevitable diabetes. Rather the prediabetic state represents an active and deleterious period of progressive beta cell deterioration and insulin resistance. Whether it is beta cell failure with impaired insulin secretion or the state of insulin resistance that is the primary instigator with the other following suit remains a point of contention.

People with prediabetes, and specifically those with IGT, appear to have worse cardiovascular and mortality outcomes. In a large European epidemiologic study of 25 000 patients all of whom had oGTT and were followed for an average of 7 years, those with IGT on a 2-h test had increased mortality (The DECODE Study Group, 1999). The risk of death was about 1.5 times greater as compared with normal glucose tolerance. On the other hand, IFG was not associated with increased mortality when adjusted for IGT. In another meta-analysis of nearly 100 000 patients followed for about 12 years, compared with normal glucose tolerance, a fasting glucose of 110 mg dl^{-1} and a 2-h oGTT glucose of 140 mg dl^{-1} carried a 1.33 and 1.58 times increased risk of cardiovascular events (Coutinho *et al*, 1999).

Prevention of diabetes

Given the apparent increase in cardiovascular events and mortality in prediabetes and the likelihood of progression to diabetes with its consequent microvascular and macrovascular complications, interventions to prevent the progression of prediabetes to diabetes and to promote reversion from prediabetes to normal glucose homeostasis have been a major point of interest and ongoing study. In one of the largest trials of diabetes prevention in individuals who had both IFG and IGT, the Diabetes Prevention Program showed that intensive lifestyle changes including diet, exercise, and a mean weight loss of 5.6 kg, decreased the development of diabetes from 11% per year in controls to 4.8% per year in the lifestyle group (Knowler *et al*, 2002). Metformin also had a significant impact on decreasing conversion to diabetes, albeit to a lesser degree of 7.8% per year.

Several other trials show that lifestyle intervention including diet and physical activity is capable of reducing the conversion rate to diabetes in those with IGT (Pan *et al*, 1997; Tuomilehto *et al*, 2001). Acarbose decreased the conversion of IGT to diabetes from 12% to 10%, and also improved reversion to normal glucose tolerance as compared with controls (Chiasson *et al*, 2002). Troglitazone taken for an average of 30 months reduced the diabetes conversion rate in Hispanic women with a history of gestational diabetes mellitus from 12% to 5.4% per year (Buchanan *et al*, 2002). In the end, the most durable effects on preventing conversion to diabetes and maintaining normal glucose tolerance are seen with lifestyle changes.

Benefits of glycemic control

The complications of diabetes include microvascular disease, macrovascular disesase, and perioral disease which will be discussed later (See Table 2). Tight glycemic control has been clearly shown to reduce microvascular complications in type 1 and type 2 diabetes, and macrovascular complications in type 1 diabetes. In the multi-center Diabetes Control and Complications Trial (DCCT), individuals with type 1 diabetes who received a more intensive insulin regimen for 6.5 years and achieved an average HbA_{1C} of 7 had a decrease in retinopathy, nephropathy, and neuropathy (The DCCT Research Group, 1993). Benefits were seen

Table 2 Chronic and acute complications of diabetes

Chronic complications of diabetes
Microvascular
Retinopathy
Impaired vision, blindness
Nephropathy
Proteinuria, chronic kidney disease, dialysis
Neuropathy
Peripheral: sensory (pain, numbness, paresthesias) and motor neuropathy
Autonomic: gastroparesis, postural hypotension, impotence
Macrovascular
Coronary artery disease
Myocardial infarction
Peripheral vascular disease
Claudication, ulcers, amputation
Cerebrovascular disease
Stroke
Perioral diseases
Gingivitis
Periodontitis
Xerostomia
Candidiasis
Oral lichen planus
Leucoplakia (premalignancy)
Oral cancer
Acute complications of diabetes
Hyperosmolar hyperglycemia
Diabetic ketoacidosis
Acute infections

in people both with and without evidence of microvascular disease at the start of the study. However, those with less initial microvascular burden and those treated sooner after diagnosis of type 1 diabetes, had a better response to intensive therapy. The follow-up observational extension to the DCCT, called the Epidemiology of Diabetes Intervention and Complications (EDIC) study, documented a persistence of improved microvascular outcomes in the former intensively treated group, even though the average HbA_{1C} of this group rose towards 8.0, the same HbA_{1c} as the conventionally treated group at year 5 after termination of the DCCT study (Writing Team for the DCCT/EDIC Research group, 2002). More importantly, over the course of 17 years of follow-up, cardiovascular events were reduced by 42% in the former intensively treated group (Nathan *et al*, 2005). This was the first and most rigorous evidence that controlling blood glucose impacted cardiovascular outcomes, the primary cause of death in people with diabetes.

Microvascular benefits of tight glycemic control are seen in type 2 diabetes as demonstrated by the United Kingdom Prospective Diabetes Study (UKPDS). Individuals treated with sulfonylureas or insulin who achieved an HbA_{1C} of seven had decreased retinopathy and nephropathy (UK Prospective Diabetes Study (UKPDS) Group, 1998). Thus far, there are no clinical trial data showing decreased macrovascular disease in intensively treated type 2 diabetes. However, epidemiologic or secondary analyses of data show an association between uncontrolled type 2 diabetes and worse cardiovascular outcomes. One meta-analysis of 11 prospective studies found that for every one point elevation in HbA_{1C}, there was an 18% increase in cardiovascular events (Selvin *et al*, 2004). Cardiovascular disease is the primary cause of death in diabetes, but it remains unproven as to whether tight blood glucose control improves this outcome in type 2 diabetes.

Based on the above studies, there is no lower limit to the beneficial effects of a reduced HbA_{1C}; positive outcomes on complications are seen all the way down to an HbA_{1C} of 6. The main limiting factor to tight glycemic control however, is the risk of hypoglycemia. The goal HbA_{1C} according to the ADA is $<7\%$, but for many individuals, tighter control with an HbA_{1C} approaching 6% or less is appropriate as long as hypoglycemia is not a significant actor. Glucose goals include a fasting level of 90–130 mg dl^{-1} and postprandial level <180 mg dl^{-1}.

Treatment of type 2 diabetes

Up until recently, people with diabetes had been managed for decades with a limited number of agents including sulfonylureas, pork and beef insulins, and metformin. Medical management of type 2 and type 1 diabetes has changed dramatically in the past 5–10 years with the availability of new classes of oral medications, injectable medications, recombinant human insulins, and novel insulin delivery systems. This armamentarium provides a multitude of options that allows the Endocrinologist a great deal of flexibility to tailor each individual's diabetes regimen, but may leave other practitioners who do not regularly prescribe these agents feeling bewildered. As all individuals with diabetes require oral or dental evaluation and many will develop oral pathology that requires intervention, a basic understanding of diabetes management is requisite for appropriate peri-procedural management by the oral medicine physician.

Initial choice of treatment of type 2 diabetes hinges on the blood glucoses and HbA_{1C} on presentation. Lifestyle changes are encouraged for all with the goal being increased physical activity, improved nutrition, and weight loss as appropriate; improvements in insulin sensitivity, glycemic control, and cardiovascular risk factors, i.e., blood pressure and cholesterol, will ensue. However, the vast majority of patients will have difficulty maintaining lifestyle changes or will not reach goals with lifestyle alone and will require pharmacologic treatment. Severe or symptomatic hyperglycemia warrants initial insulin treatment. Less severe degrees of hyperglycemia can be treated with oral medication. Each oral medicine reduces HbA_{1C} by about 1–2%. (See Table 3 for a summary of diabetes medications.)

Metformin is the initial medication of choice in a patient who has no significant end organ disease (cardiomyopathy, renal insufficiency, cirrhosis, emphysema, and alcoholism) and is younger than 80 years old. It acts by turning off hepatic gluconeogenesis and possibly also by improving insulin sensitivity in muscle and adipose tissue. The main limiting factor in metformin's use is gastrointestinal side effects which can be averted by starting at a low dose, dosing it with meals, and titrating slowly. The fear of lactic acidosis, which is exceedingly uncommon with metformin (Salpeter *et al*, 2006) in both clinical trials and real world practice (Emslie-Smith *et al*, 2001), is largely based historically in the high incidence of cases with phenformin, a biguanide that is no longer available. When used alone, metformin does not cause hypoglycemia.

Sulfonylureas, or insulin secretagogues, are very useful in lowering HbA_{1C}, but have hypoglycemia and weight gain as a side effect. Elderly patients and those with impaired renal function are particularly vulnerable to hypoglycemia, especially with glyburide. While sulfonylureas are potent and typically reduce HbA_{1C} by about 1–2.5%, they are also more likely to fail as monotherapy over time as compared with metformin or thiazolidinediones (TZDs) (Kahn *et al*, 2006).

Thiazolidinediones, including pioglitazone and rosiglitazone, have been the center of much attention over the past several years, but recent findings have dissipated this enthusiasm. TZDs are peroxisome proliferator – activated receptor γ agonists that induce transcription factors in peripheral tissues to increase the sensitivity to insulin. The strong interest in the TZDs, which was based on the anti-inflammatory effects and potential to preserve beta cells, has waned in the face of trial data which point more towards enhanced insulin sensitivity as the mode of action. The ADOPT study showed better persistence of glycemic control with rosiglitazone

Table 3 Diabetes medications, mechanisms of action, side effects, and peri-procedure managaement of medications

Drug	*Mechanism*	*Side effects/contraindications/ cautions*	*Peri-procedure management (NPO for procedure)*
Metformin	Decrease hepatic glucose production Increase insulin sensitivity	**S/E:** gastrointestinal **C/I:** end organ disease: renal failure, congestive heart failure, active liver disease/cirrhosis, emphysema; alcohol abuse; age > 80 (unless have normal creatinine clearance)	Take last dose 2 days before surgery
Sulfonylurea Glimepiride Glipizide Glyburide (including long acting formulations)	Increase insulin secretion	**S/E:** hypoglycemia **Caution:** severe renal insufficiency & elderly	Take last dose on the morning of the *day before* sugery
Thiazolidinediones Pioglitazone Rosiglitazone	Increase insulin sensitivity in adipose, muscle, and liver	**S/E:** weight gain, edema **C/I:** advanced heart failure (AHA class III or IV), acute liver disease **Caution:** ischemic heart disease	Continue medication
Meglitinides Repaglinide Nateglinide	Short-acting secretagogues used at meals Increase insulin secretion	**S/E:** hypoglycemia (if PO intake insufficient) **Caution:** severe renal insufficiency with nateglinide	Take last dose with last meal
α-Glucosidase inhibitors Acarbose Miglitol	Delay glucose absorption in intestine by inhibiting conversion of disaccharides to monosaccharides	**S/E:** gastrointestinal, hypoglycemia if PO insufficient **C/I:** creatinine > 2 mg dl^{-1}	Take last dose with last meal
Basal insulin Glargine Detemir NPH	Increase glucose uptake by muscle, adipose, and liver Decrease hepatic gluconeogenesis & glycogenolysis	**S/E:** hypoglycemia, weight gain	**Type 1 DM:** Glargine or Detemir: take 80–100% of usual dose (bedtime or morning) Insulin pump: for prolonged procedure, can not continue insulin pump; seek advice of Endocrinologist for SC insulin regimen **Type 2 DM:** Glargine or Detemir: take 2/3 of usual dose (bedtime or morning) NPH: take full dose night before, take 1/2 of usual dose on morning of surgery
Prandial (mealtime) insulin Aspart Lispro Glulisine Regular insulin	Increase glucose uptake by muscle, adipose, and liver Decrease hepatic gluconeogenesis & glycogenolysis	**S/E:** hypoglycemia (if not matched to carbohydrate intake), weight gain	Take last dose with last meal Can use correction dose on the morning of surgery to bring a high glucose down to normal
GLP-1 analogue Exenatide	Increase insulin secretion Decrease glucagon Delay gastric emptying Decrease appetite	**S/E:** nausea, vomiting, weight loss **Caution:** not to be used in gastroparesis; may need to reduce oral secretagogue dose	Take last dose with last meal
DPP-4 inhibitor Sitagliptin	Inhibits enzyme that breaks down GLP-1	**Caution:** associated with UTIs, nasopharyngitis, and headaches. Adjust dose for renal insufficiency.	Take last dose on day before surgery
Amylin analogue Pramlintide	Decrease post prandial glucose by: Decrease glucagon Delay gastric emptying Decrease appetite	**S/E:** hypoglycemia, nausea/vomiting **Caution:** need to reduce insulin dose	Take last dose with last meal

GLP-1, glucagon like peptide-1.

compared with glyburide over 4 years, but was not much better than metformin, with attainment of final $HbA_{1C} < 7$ by 40%, 36%, and 26% of those on rosiglitazone, metformin, and glyburide, respectively (Kahn *et al*, 2006). The DREAM study showed that rosiglitazone decreased conversion to diabetes in patients with impaired glucose homeostasis, from 26% to 11.6% over 3 years (The DREAM Investigators, 2006). Evidence for durability of a glycemic effect does not necessarily translate into better microvascular and

macrovascular outcomes for a particular drug. As such, a recent meta-analysis of 42 trials found a statistically significant increase in myocardial infarction with rosiglitazone, 1.4 times that of non-rosiglitazone users (Nissen and Wolski, 2007). A trial that is underway in Europe to answer the question of rosiglitazone's cardiac safety, revealed preliminary data on 4500 patients followed for nearly 4 years, and showed a non-significant trend towards increased risk of myocardial infarction (Home *et al*, 2007). In addition to the above findings, side effects such as weight gain and fluid retention are tempering the use of TZDs in clinical practice.

Some oral agents are useful for control of postprandial glucose excursions and are administered at the start of a meal. Acarbose and miglitol are α-glucosidase inhibitors, which inhibit intestinal enzymes that break down carbohydrates into monosaccharides, thereby delaying absorption of carbohydrates. Though they are only able to reduce HbA_{1C} by 0.6–1.3 %, they are a non-toxic option when a patient is almost at goal glycemic control and when postprandial elevations are the main offender. Unfortunately, gastrointestinal side effects like flatulence and diarrhea limit their use. Starting at low doses and titrating slowly is one means of introducing acarbose or miglitol into a patient's regimen. The meglitinides, repaglinide and nateglinide, are short-acting insulin secretagogues, which are used to control postprandial blood glucose, with average HbA_{1C} lowering of 1.5 for the more potent repaglinide (Gerich *et al*, 2005; Rosenstock *et al*, 2004), and with less hypoglycemia than sulfonylureas.

Despite the wide number of choices available for the treatment of diabetes, glycemic goals are not being met in many patients. Between 1998 and 2002, 30% of people with diabetes surveyed by NHANES had an $HbA_{1C} > 8\%$, while only 50% were at goal with an $HbA_{1C} < 7\%$ (Resnick *et al*, 2006). This failure to meet glycemic goals has multiple causes, including the difficulties in maintaining healthy lifestyle changes, medication side effects, resistance to insulin initiation, and medication failures. New classes of pharmaceuticals have been generated in an attempt to prevent the inexorable beta cell deterioration that is par for the course in diabetes and to promote weight loss.

Intense zeal over glucagon like peptide-1 (GLP-1) analogues has been driven by the benefits of weight loss and potential beta cell preservation. GLP-1 is a gastrointestinal hormone normally secreted during meals. The only available GLP-1 anologue, exenatide, enhances insulin secretion, reduces glucagon (a counter-regulatory hormone that raises blood glucose) secretion, delays gastric emptying, and reduces appetite via CNS effects (Drucker and Nauck, 2006). Its actions on the pancreas are dependent on glucose levels, so it does not cause hypoglycemia on its own. Although the average HbA_{1C} reduction is at most 0.5–1% and the medication is costly, it may be a useful adjunct in an overweight or obese patient who is already on several oral medications with an HbA_{1C} that is approaching goal, i.e., $HbA_{1C} = 8$, especially if the patient is not willing to start insulin. The average weight loss on exenatide is 1.5–3 kg in < 1 year, with some patients showing a more robust response. It comes in an easy-to-use prefilled pen device that is injected twice daily before meals, and should be titrated slowly as it can cause nausea. Longer acting (once daily and once weekly) injections of the GLP-1 analogues may be more acceptable to patients and are likely to become available in the near future.

Sitagliptin is an oral medication that belongs to the dipeptidyl peptidase 4 (DPP-4) inhibitors, a class which raises GLP-1 levels by blocking the enzyme which degrades it. It achieves HbA_{1C} reductions of about 0.8% but does not bring about weight loss; this may be due to an only modest elevation in GLP-1 as compared with the supra-physiologic levels achieved with exenatide injections. Long term safety of this new class still needs to be investigated, especially in light of a recent meta-analysis showing an increase in nasopharyngitis, urinary tract infections, and headache with DPP-4 inhibitors (Amori *et al*, 2007).

Insulin therapy in type 2 diabetes is typically started if glycemic goals are not met with oral medications, end organ disease or side effects prohibit use of oral medications, or acute hyperglycemic decompensation occurs. Basal insulin, or long acting insulin, is typically the first that is started with the initial goal of normalizing fasting glucose in the morning. Glargine (Lantus) and detemir (Levemir) are both long acting insulins with a duration of action of approximately 24 h, though more variable for lower doses of detemir. A more antiquated means of maintaining basal insulin is with twice daily Neutral Protamine Hagedorn (NPH) insulin, which causes peak and troughs in insulin levels and therefore more hypoglycemia. If fasting glucose is at goal, but glucose during the postprandial or premeal period is elevated, then rapid acting insulins can be added at mealtime. These insulins start to work within 15 min and act for 3–4 h making them ideal for mealtimes; they include aspart (Novolog), lispro (Humalog), and glulisine (Apidra). Premixed insulins, like 70/30 or 50/50 mix, include both an intermediate acting insulin, like NPH or aspart protamine, and a short-acting insulin, like aspart; they are administered before the morning and evening meal. Though it requires less frequent injections, premixed insulin provides less physiologic insulin levels, increases hypoglycemia, and impedes flexibility in dosing, i.e., any increase in the dose leads to an increase in both the basal and the bolus insulin.

Treatment of type 1 diabetes

Treatment of type 1 diabetes has been revolutionized by the availability of more physiologic insulins, as described earlier, and by better insulin delivery systems. The options include multiple injections per day, i.e., 3–6 injections, with a basal-bolus regimen, or continuous subcutaneous insulin infusion using an insulin pump. The insulin pump is appropriate for motivated individuals, allows for great flexibility (with ability to vary the basal insulin rate and the release of mealtime insulin depending on the food eaten), but requires significant

effort and understanding of carbohydrate counting and pump programming on the part of the patient.

Insulin use has become much more convenient, as it comes in easy-to-use disposable pen devices which hold a total of 300 units, do not require refrigeration while in use, and thus can be carried on one's person. As compared with the traditional insulin syringe and needles, pen devices do not require an individual to draw up insulin, have more precision in dialing up insulin dose, are more discreet, and may be less stigmatizing for the individual to use in public (Magnotti and Rayfield, 2007).

Optimization of cardiovascular risk factors

Controlling blood pressure and cholesterol clearly improves cardiovascular outcomes, including myocardial infarction and stroke, and reduces mortality in people with diabetes [UK Prospective Diabetes Study (UKPDS) Group, 1998; Hansson *et al*, 1998]. Blood pressure control also reduces the microvascular complications of nephropathy and retinopathy. UKPDS demonstrated a 12% reduction in diabetes related complications (macrovascular and microvascular) and a 15% reduction in deaths for every 10 mmHg decrease in systolic blood pressure over 10 years (Adler *et al*, 2000). The blood pressure goal of less than 130/80 can be achieved with ACE-inhibitors, angiotensin receptor blockers, thiazide diuretics and other agents. The primary cholesterol goal is an LDL of <100 mg dl^{-1}, and can be accomplished using statins. One study showed cardiovascular benefit of statin use in all people with diabetes regardless of the baseline LDL (Collins *et al*, 2003). In higher risk individuals with documented CAD the goal is now approaching 70–80 mg dl^{-1} (LaRosa *et al*, 2005). Lifestyle changes including diet and exercise should always be incorporated into the management of these risk factors.

Hospital management of diabetes

Management of diabetes in the hospital has until only recently been seen as a secondary objective. However, accumulating evidence points to increased infections, other morbidities, and most importantly, increased mortality, in postoperative patients and critically ill patients with hyperglycemia. Rigorous data from a large randomized trial showed reduced mortality by almost half and decreased morbidity (sepsis, renal failure, polyneuropathy, prolonged ventilation) in surgical intensive care patients treated with insulin infusion to a goal glucose of 80–110 mg dl^{-1} (Van Den Berghe *et al*, 2001). A large observational cohort study also showed a 66% reduction in sternal wound infections in open heart surgery patients treated to goal glucose of 150–200 mg dl^{-1} using intravenous insulin *vs* subcutaneous insulin (Furnary *et al*, 1999). Whether the improved outcomes are due to the correction of hyperglycemia and its negative effects on immunity, i.e., leukocyte function (Bagdade *et al*, 1974; Perner *et al*, 2003) and wound healing, or the administration of insulin, which may have pluripotent properties including anti-inflammatory (Dandona *et al*, 2001; Aljada *et al*, 2002), vasodilatory (Steinberg *et al*, 1994), and anti-platelet effects (Trovati *et al*, 1997; Worthley *et al*, 2007), is still unknown, but it may be due to a combination of the above. There are no randomized control data demonstrating a benefit for tight glycemic control in patients on the general medicine wards, but the goals as set forth by the ADA echo the findings of the ICU trials, with preprandial glucose of 90–130 mg dl^{-1} and postprandial glucose <180 mg dl^{-1}.

The most important questions to ask when managing a patient with diabetes who will undergo a dental procedure or oral surgery are: (i) Does the patient have type 1 or type 2 diabetes? (ii) What diabetes medications is the patient taking, including the amounts and types of insulin? (iii) How good has the metabolic control been, i.e. what is the HbA_{1c} and blood glucose at home? Patients with type 1 diabetes are completely dependent on exogenous insulin and can succumb to ketoacidosis if the insulin administered does not meet their metabolic requirements which will certainly increase with stressors like infection or surgery. Individuals with type 2 diabetes, for the most part, are capable of making enough insulin to avoid ketoacidosis; however, some may have little capacity for insulin secretion, especially if they have long standing diabetes for more than 20–25 years and are taking insulin injections. Brief guidelines on managing diabetes medications before a procedure that requires NPO status are listed in the last column of Table 1. Individuals with type 1 diabetes undergoing major surgery require intra-operative glucose monitoring and insulin therapy. It would be prudent to consult with the patient's Endocrinologist before minor and major surgery if the patient is taking insulin or has type 1 diabetes, and before major surgery in all patients with diabetes.

Diabetes and oral diseases

Diabetes is a risk factor for oral pathology including gingivitis, periodontitis, candidiasis, oral lichen planus, premalignant lesions like leucoplakia, and oral malignancies (Petrou-Amerikanou *et al*, 1998; Ujpa'l *et al*, 2004; Goutzanis *et al*, 2007). Poor control and increased duration of diabetes are associated with more severe periodontal disease. Because of this strong association, Löe (1993) characterized severe periodontitis as the sixth complication of diabetes. In a large population based study using NHANES data, individuals with poorly controlled diabetes, as measured by an HbA_{1C} greater than 9, were three times more likely to have severe periodontitis than normals (Tsai *et al*, 2002). Smoking further increases the risk for periodontitis in people with diabetes. Periodontal disease in and of itself may contribute to systemic inflammation and worsening insulin resistance and diabetes through the generation of inflammatory cytokines (Loos *et al*, 2000). A study in Pima Indians with diabetes who were not insulin-requiring, showed that severe periodontitis at baseline is associated with worsening glycemic control over time (Taylor *et al*, 1996).

All of the above evidence points to a vicious cycle of diabetes and periodontitis exacerbating one another. Moreover, the inflammatory state of periodontitis may contribute to acceleration of cardiovascular disease, the number one cause of death in diabetes. In a prospective study of 630 Pima Indians with diabetes who were followed for more than 11 years, there was an increased mortality attributed to periodontal disease. Severe periodontitis was an independent risk factor for death due to ischemic heart disease or renal disease, increasing the risk by 3.2 times as compared with those with none, mild, or moderate periodontitis (Saremi *et al*, 2005).

Multiple studies have examined the role of improved oral hygiene in diabetes control, some bearing positive results and others negative results (Grossi *et al*, 1997; Stewart *et al*, 2001; Rodrigues *et al*, 2003; Promsudthi *et al*, 2005; Jones *et al*, 2007). To date, it is not certain whether oral intervention improves glycemic control. However, given the potential link between periodontal disease, diabetes, and cardiovascular disease, aggressive management of oral health and regular follow-up seems a reasonable approach in people with diabetes. The final culmination of years of untreated periodontal disease is an edentulous state, which may lead to nutritional deficiencies, psychosocial consequences, and deterioration in quality of life even in those with dentures (Sheiham *et al*, 2001a; Allen and McMillan, 2003). For instance, in the UK National Diet and Nutrition Survey of people aged 65 years and over, dentate individuals had higher intake of protein, fiber, calcium, iron, niacin, and vitamin C than edentulous individuals, and this was supported by blood levels of vitamins (Sheiham *et al*, 2001b). Poor nutritional intake and unhealthy food choices may in turn exacerbate diabetes, obesity, and cardiovascular disease.

Conclusion

Diabetes is a prevalent disease that causes multiple comorbidities and increases the risk of death in those whom it affects. Periodontal disease and other oral pathologies are complications of diabetes that will bring these patients to the attention of oral health practitioners. Many of these individuals will have undiagnosed diabetes or uncontrolled diabetes, and the oral medicine physician can be critical in making the diagnosis, counseling the patient in the importance of diabetes control, and referring the patient to an endocrinologist for further management. Furthermore, aggressive management of periodontal disease in a patient with diabetes may diminish the inflammatory milieu's detrimental effects on diabetes control and the cardiovascular health of the patient. For these reasons, the oral medicine physician can have a major impact on both the diagnosis and control of this common disease, thereby improving the lives of individuals with diabetes.

Author contributions

Maria Skamagas and Tracy Breen drafted the paper and Derek LeRoith edited the paper.

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