
Position Paper

Diabetes and Periodontal Diseases*

THIS POSITION PAPER ON DIABETES MELLITUS was prepared by the Research, Science and Therapy Committee of The American Academy of Periodontology. It is intended to: 1) update members of the dental profession on the diagnosis and medical management of patients with diabetes mellitus; 2) summarize current knowledge on the relation between diabetes mellitus and periodontal diseases; 3) provide an overview of factors in diabetic patients relevant to understanding the pathogenesis of periodontal diseases in these subjects; 4) outline special considerations associated with treatment of periodontal diseases in diabetic patients; and 5) discuss possible approaches to the management of diabetic emergencies in the dental office.

Reliance on this position paper in patient management will not guarantee a successful outcome. Periodontal diseases often involve numerous and complex causes and symptoms. Ultimately, decisions regarding the diagnosis and treatment of disease in an individual patient must be made by the treating practitioner in light of the specific facts presented by that patient. *J Periodontol 1996;67:166-176.*

DIAGNOSIS AND MEDICAL MANAGEMENT OF DIABETES MELLITUS

Diabetes mellitus (DM) encompasses a heterogeneous group of disorders with the common characteristic of altered glucose tolerance or impaired lipid and carbohydrate metabolism. DM develops from either a deficiency in insulin production or an impaired utilization of insulin. Based upon these 2 conditions, diabetes mellitus can be divided into 2 main types: insulin-dependent diabetes mellitus (IDDM) or Type I diabetes, and non-insulin dependent diabetes mellitus (NIDDM) or Type II diabetes. Diabetes insipidus is a condition unrelated to diabetes mellitus. Diabetes insipidus results from an overproduction of a renal hormone (aldosterone) with excessive urine production and polyuria, but does not have any effect on blood glucose levels.

IDDM is caused by the destruction of the insulin-producing β cells of the pancreas. The pathophysiology may involve an autoimmune or virally-mediated destructive process.^{3,4} In theory, cells are destroyed when genetically predisposed individuals are subjected to a triggering event such as viral infection which induces a destructive autoimmune response. Onset is often abrupt and the condition may be unstable and difficult to control.^{5,6}

NIDDM results from defects in the insulin molecule or from altered cell receptors for insulin and represents impaired insulin function (insulin resistance) rather than deficiency.⁴ However, insulin production may be diminished later in the disease and insulin supplementation may become

necessary.⁷ Onset of symptoms is generally gradual and patients are less likely to develop ketoacidosis. NIDDM patients are often obese and their glucose intolerance typically can be improved with control of diet and body weight. Additionally, oral hypoglycemic agents are often required.⁷

It is estimated that 12 to 14 million individuals in the United States have diabetes, with only half of the affected individuals diagnosed.⁸ NIDDM constitutes 85 to 90% of diabetic cases, while IDDM constitutes 5 to 10%. A third category of diabetes mellitus is disease secondary to or associated with other conditions such as gestational diabetes which is a condition associated with pregnancy. This last category accounts for 2 to 5% of the total number of diabetic cases. In contrast to the general population prevalence of 5%, the prevalence of NIDDM in individuals 65 years and older is 8.6%.⁸⁻¹⁰ With improved screening and diagnostic tools, it can be expected that an increasing percentage of the population will be diagnosed as diabetic.

The American Diabetes Association and World Health Organization have proposed use of uniform diagnostic terms to categorize diabetes based on the physiological basis of disease.¹¹ These categories are NIDDM, IDDM, impaired glucose tolerance, and gestational diabetes. Impaired glucose tolerance as a diagnosis describes a condition where blood glucose levels in a subject are intermediate between normal and overt diabetes. The American Diabetes Association has recommended elimination of the following terms: latent, subclinical, and chemical diabetes mellitus; prediabetes; potential diabetes; and adult-onset, maturity-onset, and juvenile-onset diabetes.¹¹

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General Signs and Symptoms

The classic signs and symptoms of DM include the triad of polyuria, polydipsia, and polyphagia together with pruritis (skin, rectum, or vagina), weakness, and fatigue. These indicators of diabetes are more common in IDDM, but occur to varying degrees in NIDDM. Weight loss may occur, especially in IDDM. Nausea and vomiting are commonly found with uncontrolled IDDM and are associated with increasing ketoacidosis. Restlessness, irritability, and apathy may become evident.^{7,12} These signs and symptoms may be reversible with early diagnosis and effective therapy.

Complications

The general signs and symptoms of DM are the direct result of hyperglycemia. Likewise, systemic complications of DM are associated with prolonged hyperglycemia. Diabetic retinopathy is one of the leading causes of blindness in the United States. Accelerated atherosclerotic cerebrovascular, cardiovascular, and peripheral vascular diseases may occur due to abnormal lipid metabolism and muscle wasting. Myopathies can produce progressive weakness and diminished exercise tolerance. Sensory neuropathies result in peripheral loss of sensation and dysesthesias sometimes followed by gastrointestinal neuropathy and autonomic nerve degeneration leading to orthostatic hypotension. Many individuals also develop progressive renal dysfunction that can lead to end-stage renal disease. These patients may require renal dialysis or transplantation. Diabetic nephropathy can result in an increased incidence of hypertension.^{7,12}

Medical Treatment

Treatment of diabetes mellitus is designed to lower blood glucose levels and prevent the complications associated with the disease. Diet control has been used for many years to control NIDDM by reducing the intake of refined sugars and high fat foods, and by minimizing excess body fat.^{13,14} Oral hypoglycemic drugs stimulate insulin release from pancreatic β cells and promote insulin uptake in body tissues. These drugs are all members of the sulfonylurea group but have varied duration of action. Short-acting agents such as tolbutamide, tolazamide, and acetohexamide are maximally effective for up to 24 hours, while long-acting agents such as chlorpropramide, glipizide, and glyburide are effective for up to 36 hours.¹⁵

In cases of decreased insulin production, insulin for parenteral administration is available in multiple formulations to control rate of action. Injectable insulin is available primarily in 3 forms: short-acting forms (regular and semilente); intermediate-acting forms with 24-hour duration of activity (isophane lente and NPH [neutral protamine Hagedorn]); and a long-acting form with a duration of

activity for more than 36 hours (ultralente).¹⁶ Modern insulin therapy often involves the use of a combination of short- and intermediate-acting agents with or without long-acting insulin. Insulin is available from 3 sources: bovine, porcine, and human made by recombinant DNA technology. Human insulin has a more rapid onset and shorter duration of activity than porcine insulins, whereas bovine insulins have the slowest onset and longest duration of activity.¹⁶ Different types and forms of insulin have different pharmacological properties and should only be changed under the direction of a health professional with expertise in diabetes.¹⁶ Experimental treatments for DM now under investigation include the use of the immunosuppressive drug cyclosporin, pancreas transplants, or transplantation of β cells from the pancreas.^{6,7}

Conclusive evidence of the role of glycemic control in prevention of diabetic complications was provided by the Diabetes Control and Complications Trial (DCCT).¹⁷ This multi-center study of 1,441 Type I DM patients compared complications in two cohorts; one using conventional insulin regimens (one or two injections per day), and the other on a tight control regimen (3 or more daily injections or use of an insulin pump). Over a 6.5 year period, the incidence of diabetic eye, kidney, and nerve complications were significantly reduced in the tight control cohort. For individuals with no evidence of retinopathy, the adjusted mean risk for the development of retinopathy was reduced by 76% in the tightly controlled group. The progression of retinopathy in patients with mild retinopathy at the start of the study was slowed by 54%. Intensive therapy reduced the occurrence of microalbuminuria and albuminuria by 39% and 54% respectively. Clinical neuropathy was reduced by 60%. The chief adverse event associated with intensive therapy was a 2- to 3-fold increase in severe hypoglycemia. Thus, IDDM patients with periodontal treatment needs must be evaluated for risk of hypoglycemia during dental procedures based on their history and insulin regimen.

IDDM patients are always at risk of experiencing severe hypoglycemia or shock due to insulin excess, but the risk of either of these emergency complications is reduced by effective sustained metabolic control.⁵ The use of blood glucose monitors by patients is widespread, and is of considerable benefit in adjusting insulin dosage to meet daily requirements. The diabetic patient's monitor is of considerable value to the practitioner treating patients receiving insulin therapy.

Tests Used for Determining Blood Glucose Levels

The primary methods used to diagnose diabetes mellitus and monitor blood glucose levels have been fasting blood glucose, a combination of fasting blood glucose plus a 2-hour test after glucose loading (2-hour post-prandial), and oral glucose tolerance tests (Table 1). These tests,

Table 1. Diagnostic Criteria for Diabetes¹¹

Diabetes mellitus: values for adults

1. Unequivocal elevation of plasma glucose (PG): ≥ 200 mg/dl and classic symptoms of diabetes, including polydipsia, polyuria, polyphagia, and weight loss.
2. Fasting plasma glucose (FPG): ≥ 140 mg/dl on 2 occasions.
3. FPG < 140 mg/dl and 2 oral glucose tolerance tests (OGTTs) with the 2-h PG ≥ 200 mg/dl and one intervening value ≥ 200 mg/dl after a 75-g oral glucose intake.

Diabetes mellitus: values for children

1. Classic symptoms as with adults, with random PG ≥ 200 mg/dl.
2. FPG ≥ 140 mg/dl on 2 occasions and 2 OGTTs with the 2-h PG and one intervening value ≥ 200 mg/dl (loading with 1.75 g/kg to maximum of 75-g glucose).

Impaired glucose tolerance

1. Abnormality in glucose levels intermediate between normal and overt diabetes.
2. FPG < 140 mg/dl and 2-h PG ≥ 140 and < 200 mg/dl with one intervening value ≥ 200 mg/dl after a 75-g glucose load.

Gestational diabetes mellitus

1. Diabetes established by criteria of either impaired glucose tolerance or adult DM.
2. OGTT may be used. Criteria for positive test are: FPG 105 mg/dl; 1-h 190 mg/dl; 2-h PG 165 mg/dl; 3-h PG 145 mg/dl.

Normal glucose values for non-pregnant females are FPG < 115 mg/dl; 2-h PG < 140 mg/dl. OGTT values between time-zero and 2-h PG < 200 mg/dl.

Results above the listed normal values, but below levels diagnostic for impaired glucose tolerance, are not diagnostic for diabetes mellitus.

though requiring exacting circumstances, clearly demonstrate the individual's capacity to regulate serum glucose levels. Evaluation of urine glucose levels has been used for many years as a screening and monitoring mechanism, but is insensitive and has been recommended that it be replaced by self-monitoring blood glucose instruments for patient self-assessment when feasible.¹⁸ The glycosylated hemoglobin test has been used as a monitoring tool, and has recently been advocated as a screening tool.¹⁹ The glycosylated hemoglobin assay measures the amount of glucose irreversibly bound to the hemoglobin molecule. This value is proportional to the blood glucose levels, and thus gives a measure of the blood glucose status over the half-life of the red blood cells, or 30 to 90 days. Glycosylated hemoglobin (also called glycated hemoglobin) normally ranges from 5.0% to 8.0%,^{19,20} but must be interpreted in the context of the range of normal values for the individual medical laboratory performing the service. Most recently, glycosylated albumin and glycosylated fructosamine have been developed as monitoring tools, although some evidence suggests that fructosamine may not be suitable for diabetes screening.¹⁹ Fructosamine levels provide assessment of glycemic control over the past 4 to 6 weeks. The normal range for fructosamine is 2.00 to 2.80 mmol/L.^{12,21}

Table 2. Quality Control for Using Self-Monitoring Blood Glucose Devices in the Outpatient Setting²¹

Personnel performing the test must be qualified through documented training.

Written procedures and policies should be developed for test performance, quality control, standardization and calibration of instruments, and reagent acquisition and storage.

Quality control must occur routinely and be documented.

A basic accession record including patient name, test and date should be maintained to correlate with documented quality control results.

Results must be periodically verified with a reference laboratory.

Dry reagent strips with a reflectance meter are commonly used by diabetic patients for home monitoring of their blood glucose levels using 1 or 2 drops of blood. This procedure is of interest to the dental practitioner since it is simple, relatively inexpensive, and of sufficient accuracy to serve as an in-office screening device for patients suspected to have diabetes, and to monitor blood sugar levels of known diabetic subjects. Self-monitoring blood glucose devices are recommended for controlled diabetic subjects and may be used prior to undergoing treatment procedures likely to impair oral dietary intake.^{6,7}

In general, self-monitoring devices must not be used to diagnose DM,²¹ and their role in large-scale screening remains undecided. The American Diabetes Association recommends the devices for insulin-treated patients, pregnancy complicated by diabetes, patients with unstable diabetes, patients with a propensity to severe ketosis or hypoglycemia, patients prone to hypoglycemia who may not experience the usual warning symptoms, patients on intensive treatment programs, and patients with abnormal renal glucose thresholds.²¹ Results obtained with instrument-analyzed strips may be more accurate than those assessed visually. Factors affecting the values obtained include hematocrit, hypoglycemic or severe hyperglycemic ranges, and reagent strip storage and age.

Quality control is essential for healthcare professionals who use self-monitoring blood glucose devices in an outpatient setting. The American Diabetes Association endorses the position of the Joint Commission on Accreditation of Healthcare Organizations that self-monitoring blood glucose devices by non-laboratory personnel must meet minimum standards as outlined in Table 2.

PERIODONTAL DISEASE AND DIABETES

The criteria for diagnosing diabetes have undergone significant changes since the early 1960s. Likewise, the diagnosis of periodontal disease has been better defined. Using refined standards for diagnosing these two disease states, several general trends are apparent. Uncontrolled or poorly-controlled diabetes is associated with increased susceptibility to oral infections, including periodontitis.²²⁻²⁶ The incidence of periodontitis increases among

diabetic subjects after puberty and as the patient population ages.²⁷⁻³⁹ Periodontal disease may be more frequent and severe in diabetic individuals with more advanced systemic complications.^{35,37,40} The increased susceptibility does not correlate with increased levels of plaque and calculus.^{28,39,41-43} Collectively, the evidence supports the theory that there is a relationship between the two diseases, especially in patients with poorly controlled diabetes mellitus or hyperglycemia.

Insulin-Dependent Diabetes Mellitus and Periodontal Disease

In initial studies to investigate a relation between periodontal disease and IDDM, the periodontal status of 263 IDDM patients was compared to 59 non-diabetic siblings and to 149 non-diabetic, unrelated controls.³⁰ No periodontal disease was found among the subjects under the age of 12 (N = 97), while 13.6% of the individuals 13 to 18 years old (N = 110) had periodontal disease. Individuals from 19 to 32 years old had a prevalence of 39% (N = 56). There was no periodontal disease found in the non-diabetic siblings of the IDDM patients, while a prevalence of 2.5% was noted in the non-diabetic, unrelated control subjects. In addition, the investigators noted that the duration of diabetes was greater in the groups with severe periodontal disease. Thus, it appears that IDDM patients have an increased risk for developing periodontal disease with age, and that the severity of periodontal disease increases with the increased duration of diabetes. Recently, 71 patients with IDDM have been studied with a 16.5 years mean duration of disease.⁴⁴ The patients were divided into poorly-controlled and well-controlled diabetic subjects based on long-term medical records. Under similar conditions of plaque control, adult subjects with poorly-controlled diabetes had lost more approximal attachment and bone than well-controlled diabetic subjects.

Non-Insulin-Dependent Diabetes Mellitus and Periodontal Disease

Studies have been done on Pima Indians, a population suffering from an extremely high prevalence of NIDDM. In the initial study of periodontal disease in this community, a cross-sectional analysis was done using periodontal attachment loss and radiographic bone loss.⁴⁵ Subjects (N = 3,219) were evaluated using a glucose tolerance test to identify diabetic subjects. Irrespective of age, subjects with diabetes had a higher prevalence of periodontal disease using either periodontal attachment loss or radiographic bone loss, indicating that diabetes is a risk factor for periodontal disease. Further studies were conducted on the dentate individuals (subjects with the 6 Ramfjord index teeth), giving a subset of 1,342 individuals.⁹

Compared to non-diabetic individuals, subjects with NIDDM were 2.8 times more likely to have periodontal disease defined by clinical attachment loss, and 3.4 times more likely defined by radiographic bone loss. The increased risk of developing periodontal disease could not be explained on the basis of age, sex, or hygiene. When prevalence of clinical attachment loss (1 or more sites \geq 5 mm) was evaluated by age, diabetic subjects age 15 to 24 had 4.8 times more periodontal disease than non-diabetic subjects, while those age 25 to 34 had 2.3 times more periodontal disease. The prevalence of periodontal disease in the three remaining age groups was marginally higher among the diabetic subjects: for diabetic patients age 35 to 44 the ratio was 1.5; for those age 45 to 54 and age 55+ the ratio was 1.1. The decreased ratio between diabetic and non-diabetic subjects was primarily due to the high prevalence of periodontal disease in non-diabetic Pima Indians (27.5% prevalence for those over 45 years of age).

In another study of the Pima Indians, the incidence and prevalence of periodontal disease were determined in 2,273 subjects 15 years of age or older.⁴⁶ The incidence was determined in a subset of 701 subjects 15 to 54 years old, with little or no evidence of periodontal disease. The prevalence of periodontal disease was 60% in subjects with diabetes, and 36% in patients without diabetes. Following these subjects for an average of 2.6 years, the rate of development of periodontal disease in diabetic subjects was 2.6 times that observed for non-diabetic patients, when age and gender were considered.⁴⁶

Attachment Loss

Attachment loss has been found to occur more frequently and more extensively in moderate- and poorly-controlled diabetic patients of both types than in those under good control.⁵¹ A Finnish study corroborated these findings; more attachment loss and approximal bone loss was found in poorly-controlled than well-controlled IDDM subjects.⁴⁴

There is also evidence suggesting that more frequent and more advanced loss of attachment may be found in patients where diabetes is of long duration.^{28,52} This correlation with the duration of diabetes is similar to that of other complications of diabetes such as nephropathy, retinopathy, neuropathy, and vascular disease. At least one study suggests a stronger correlation between periodontal breakdown and other diabetic complications such as retinopathy.⁵²

Probing Depth

Significantly more missing teeth and sextants with deep pockets were found in diabetic patients than controls using the Community Periodontal Index of Treatment Needs.⁴⁰

In a Minnesota study, 41% of diabetic patients had 1 or more sites with probing depth ≥ 4 mm compared to 16.0% reported in the 1985-86 United States Adult National Survey.⁵³ The extent (% of sites per person) of sites with a probing depth ≥ 4 mm was 5.2 for patients with diabetes compared to 1.6 for the national survey.⁵³ In another study, well-controlled diabetic subjects had 2.5% of sites with probing depths ≥ 4 mm compared to 11.2% of sites in poorly-controlled diabetic subjects, indicating worsening periodontal conditions in patients with poorly-controlled versus well-controlled diabetes.⁵¹

Gingivitis

Among the first references to diabetes and periodontal disease was an article that described the gingiva from patients with diabetes to have "sessile or pedunculated proliferations or polyps."⁴⁷ It was suggested that this gingival change was of significance in diagnosing patients with diabetes. Several studies document that gingivitis is more severe in children with diabetes than in those without the disease.^{35,48,49} Diabetic children were found to have significantly more gingival inflammation than children without diabetes with no difference in plaque scores between the two groups.³² Diabetic children with poor metabolic control had significantly higher gingival index scores than did non-diabetic controls.⁵⁰

Other Oral Manifestations

Diminished salivary flow and burning mouth or tongue are common complaints of patients with uncontrolled diabetes mellitus. Concomitant enlargement of parotid glands has been described, possibly as a result of alterations in the basement membranes of parotid ducts or other histopathologic changes.⁵⁴⁻⁵⁷ Increased glucose content also has been demonstrated in gingival crevicular fluid.^{58,59} It has been suggested that glucose in gingival fluid may result in altered plaque microflora and influence the development of periodontal disease and dental caries.⁶⁰ In addition, many diabetic subjects will be taking medications that induce oral dryness which can contribute to the xerostomic state.^{41,61,62} The xerostomia may be conducive to infection by opportunistic microorganisms such as *Candida albicans* with development of candidiasis. Oral candidiasis has been associated with poorly-controlled diabetes.⁶³

An increased incidence of dental caries has been found in association with uncontrolled or poorly-controlled diabetes in both humans and experimental animals.^{34,64-66} The bulk of available evidence, however, suggests that the well-controlled diabetic patient experiences reduced caries incidence, presumably due to dietary reductions in refined carbohydrates, effective metabolic control, and compliance with oral hygiene procedures and dental recall appointments.^{41,61,67,68}

FACTORS POTENTIALLY CONTRIBUTING TO THE DEVELOPMENT OF PERIODONTAL DISEASE IN PATIENTS WITH DIABETES MELLITUS

Polymorphonuclear Leukocyte Function

Numerous studies have identified a clear role for the polymorphonuclear leukocyte (PMN) in the maintenance of gingival and periodontal health. Reduced PMN function has been found in patients with diabetes. This impairment of function was noted in assays of PMN chemotaxis,⁶⁹⁻⁷³ adherence,⁷⁴ and phagocytosis.^{73,75-78} Studies of PMN defects suggest that this dysfunction could lead to impaired host resistance to infection.^{62,79,80}

The severity of periodontitis has been correlated with defective chemotaxis; diabetic patients with severe periodontitis had depressed PMN chemotaxis compared to those with mild periodontitis or non-diabetic subjects with severe or mild periodontitis.^{81,82} Further, decreased PMN chemotaxis has been reported in a family with a history of diabetes and severe periodontitis, suggesting that the PMN defect was of genetic origin.⁸³ A local effect has been suggested since the PMN phagocytic activity of gingival sulcular PMNs was less than that of peripheral blood PMNs and, irrespective of the diabetic state, the functional activity of PMNs collected from diseased sites was less than that at healthy sites.⁸²

PMN defects have been studied in rats chemically treated to induce diabetes.⁸⁴ Chemotactic agents, FMLP, and casein were applied atraumatically on the gingival margin of rats with chemically-induced diabetes and non-diabetic controls. Diabetes of 4, 14, and 20 days reduced the peak chemotactic response of crevicular PMNs to FMLP 45, 66, and 71%, respectively. Uncontrolled diabetes of 20 days duration reduced the peak neutrophil response to casein by 83%. Importantly, diabetic rats receiving insulin showed a reduction of only 34%. Thus, in rats it appears that the abnormalities in PMN functions can be corrected by insulin therapy.

Collagen Metabolism

Synthesis of collagen appears to be affected by glucose levels. Studies of skin fibroblasts have shown that hyperglycemic conditions have reduced cell proliferation and growth^{85,86} and reduced synthesis of both collagen^{85,87,88} and glycosaminoglycan.⁸⁹ In addition, gingival fibroblasts from diabetic patients synthesize less collagen compared to non-diabetic subjects.⁹⁰ Rats with experimentally-induced diabetes have impaired production of bone matrix components by osteoblasts and decreased collagen synthesis by gingival and periodontal ligament fibroblasts.⁹¹⁻⁹³ Tetracycline was found to ameliorate the suppressed metabolic activity of osteoblasts and periodontal ligament fibroblasts of diabetic rats.⁹³

In addition to finding decreased collagen production in association with diabetes, investigators also have found

increased collagenase activity in gingival tissue in animals.⁹¹⁻⁹³ Crevicular fluid collagenolytic activity also was increased in diabetic patients;⁹⁴ this increased crevicular fluid collagenase activity appears to be primarily of neutrophil origin. Rats raised in germ-free conditions developed elevated collagenase levels when diabetes was induced with streptozotocin.⁹⁵ Collectively, these results indicate that the increased collagenase was endogenously derived independent of bacterial factors. Interestingly, the increased crevicular fluid collagenase levels found in patients with diabetes can be inhibited *in vitro* by tetracycline.⁹⁴

Collagen in a hyperglycemic environment undergoes non-enzymatic glycosylation and cross-linking between the collagen molecules. This cross-linking of collagen significantly contributes to reduced solubility and decreases turn-over rate.^{88,96-98} Consistent with these results, diabetic gingival collagen shows decreased solubility properties. Significantly, a return to near-normal solubility of collagen can be achieved by insulin treatment.^{92,99}

Infections in Patients with Diabetes

It is generally accepted that patients with diabetes are more susceptible to the development of infections than those without diabetes. It also is believed that infections in diabetic patients are more severe than the same infection in a non-diabetic individual. However, conclusive studies supporting these clinical impressions do not currently exist. *In vitro* studies of host defense cells (specifically PMNs) from diabetic subjects show that these individuals may have impaired defense mechanisms.⁶⁹⁻⁸⁰ As previously stated, studies of PMNs from diabetic animals (streptozotocin-induced) show that insulin therapy can reverse the defective function of these cells.⁵⁴

Insulin resistance is a condition that exists during acute infections.¹⁰⁰⁻¹⁰³ This condition occurs independent of the diabetic state; e.g., non-diabetic subjects experience varying degrees of insulin resistance during acute infections. Hyperglycemia and hyperinsulinemia after oral glucose administration are the hallmark findings of insulin resistance. Significantly, insulin resistance has been found to exist for 1 to 3 weeks in non-diabetic subjects after resolution of the infection.^{104,105} The molecular basis for infection-induced insulin resistance is not clearly understood.

Vascular changes have also been recognized in patients with diabetes.¹⁰⁶ Basement membrane (BM) proteins become glycosylated in a hyperglycemic environment, with thickening and changes in the physical properties.^{96,106,107} Gingival capillaries of diabetic subjects have thickened BMs,¹⁰⁸⁻¹¹⁰ as well as disruption of the BM, collagen fibers within the BM, and swelling of the endothelium. These changes can be hypothesized to impede oxygen diffusion, metabolic waste elimination, PMN migration, and diffusion of serum factors including antibodies. Other studies have failed to show any difference in the thickness

of the basement membrane of gingival vascular tissue in diabetic patients.¹¹¹

Collectively, defects in PMN function, induction of insulin resistance (or increased insulin resistance in the diabetic subject), and vascular changes can all contribute to increased susceptibility to infection. Importantly, control of serum glucose levels appears to partly reverse these factors and should therefore be closely monitored with infections.

Wound Healing

The mechanisms responsible for compromised wound healing in individuals with diabetes are unknown. It is probable that the cumulative effects of altered cellular activities which play a part in susceptibility to infections also affect wound healing. In addition, decreased collagen synthesis by fibroblasts and increased collagenase production found in diabetic patients play a role in wound healing. Glycosylation of existing collagen at the wound margins results in reduced solubility and delayed remodeling of the wound site. In addition, the increased collagenase can readily degrade the newly synthesized, less completely cross-linked collagen, further contributing to defective wound healing.^{87,112}

The late inflammatory response to wound healing has been found to be altered in diabetes.¹¹³ Wound chambers in normal and streptozotocin-induced diabetic mice showed marked differences in both cellular infiltration (PMNs) and cytokine levels (tumor necrosis factor and interleukin-6). There were no differences in any parameters on days 1 or 3. On day 7, tumor necrosis factor was not different between groups, but the number of PMNs had failed to increase in the diabetic mice ($P < 0.05$ versus normal mice), and the interleukin-6 level had decreased in diabetic mice ($P < 0.05$ versus normal mice).

The connective tissue response has been studied in a wound healing model. Skin wound healing was compared in 3 groups of rats: normal, genetically diabetic, and streptozotocin-induced diabetic.¹¹⁴ Insulin was administered daily to all diabetic animals. Full-thickness dorsal skin wounds were analyzed biomechanically for strength, toughness, and elasticity at 1 and 3 weeks after wounding. Wounds from normal controls were the strongest, toughest, and least compliant, while wounds in genetically diabetic rats were the weakest and had the lowest elasticity. Wounds in streptozotocin-induced rats were intermediate for all parameters tested.

The mitogenic activity of platelets from patients with diabetes has been found to be decreased; platelets from diabetic subjects induced significantly less proliferation of fibroblasts than did platelets from non-diabetic subjects.¹¹⁵ An association between reduced mitogenic activity and decreased wound activity has not been determined, but would seem to be related.

Bacterial Associations

Induction of experimental diabetes in rats is known to cause a shift in subgingival bacteria to a periodontopathic flora predominated by Gram-negative rods and filaments with subsequent deepening of periodontal pockets.¹¹⁶ In a longitudinal study of diabetic subjects, the percentage of streptococci, a group of bacteria associated with periodontal health, increased after improvement in the metabolic control of the diabetic state.¹⁰⁷

Capnocytophaga species predominate in most periodontal lesions of young IDDM patients, averaging 24% of the cultivable flora in one report.¹¹⁷ *Actinobacillus actinomycetemcomitans* was found in cultures of the subgingival flora in 3 of 9 diabetic subjects with periodontitis but in none of those with gingivitis or normal periodontal tissues. Black-pigmented Gram-negative *Bacteroides* and *Fusobacterium* species comprised only a small percentage of the periodontal isolates. A number of subsequent studies have failed to show any significant association of *Capnocytophaga* species with periodontal disease in IDDM patients.^{107,117-119}

The composition of the periodontal microflora found in periodontally-diseased sites of NIDDM patients appears to be similar to that found in chronic adult periodontitis. *Prevotella intermedia*, *Campylobacter rectus*, and *Porphyromonas gingivalis* have been found as the 3 most predominant pathogens in subgingival dental plaque of NIDDM patients.¹¹⁸ The cultivable flora study demonstrated that 67 to 88% of the patients were positive for these species. Immunofluorescence microscopic examination revealed that *A. actinomycetemcomitans* was present in small numbers in 2 of 16 NIDDM subjects. Higher levels of *P. intermedia* have been reported in diseased versus healthy periodontal sites in IDDM.¹⁰⁷ The occurrence of *A. actinomycetemcomitans* and *P. gingivalis* was similar to that found in chronic adult periodontitis.

DENTAL THERAPY IN THE PATIENT WITH DIABETES MELLITUS

Considerations for Treating the Diabetic Patient

The initial dental therapy for patients with DM, as with all patients, must be directed towards control of acute oral infections. At the same time, communication must be established with the patient's physician so that a plan can be developed to obtain control of blood glucose levels. It is important to advise the physician of the periodontal status, since the presence of infections including advanced periodontal disease may increase insulin resistance and contribute to a worsening of the diabetic state.^{104,105,120,121} On occasion, oral infections may even be life-threatening to diabetic patients.^{26,122,123} Insulin requirements are reduced in some IDDM subjects following periodontal therapy.^{30,120,121,124} In a pilot study, reduction of inflam-

mation in poorly-controlled diabetic subjects (measured by bleeding on probing) correlated with reduced blood glucose levels.¹⁷⁰

Periodontal status in patients with DM has been related to diabetic control over a 2-5 year period.⁵¹ Seventy-five patients with DM were studied (59% IDDM and 41% NIDDM). Blood glucose was monitored using glycosylated hemoglobin. It was found that the patients with poor diabetic control had significantly more calculus, while both groups had similar levels of plaque control. Significantly more sites had attachment loss ≥ 3 to 5 mm compared to controls. Multiple regression analysis indicated calculus and long-term control of diabetes were significant variables when probing depths ≥ 4 mm were used as the dependent variable. The prevalence of severe attachment loss increased with decreasing control of diabetes.

The short-term response of controlled diabetic subjects to non-surgical periodontal therapy appears equivalent to that of normal individuals;¹²⁵ 3 to 4 months after oral hygiene instructions and scaling and root planing there was approximately a 50% reduction of gingival inflammation (bleeding on probing), and a 33% to 50% reduction in probing depths (4 to 5 mm). There was no statistically significant difference in responses between the controlled diabetic and non-diabetic individuals in the study. The response of the controlled diabetic patient to surgical therapy is currently unknown.

Timing of Treatment for the Diabetic Patient

Patients with well-controlled NIDDM or IDDM can be treated similarly to non-diabetic patient for most routine dental needs. Procedures should be short, atraumatic, and as stress-free as possible. Patients should be instructed to take their medications as prescribed and to continue diet control and self-monitoring of glucose levels during the course of dental treatment. Patients should eat a normal breakfast before dental appointments to prevent hypoglycemia. Early morning appointments are preferred because levels of endogenous corticosteroids are generally higher at that time and stressful procedures can be better tolerated. If conscious sedation is needed for a potentially stressful procedure, or if an extensive surgical procedure is planned, the patient may be required not to eat breakfast and special dietary and medical attention may be necessary. On their physician's orders, NIDDM patients may be instructed to omit hypoglycemic medication for the day of the procedure followed by a return to normal dosage the following day. IDDM patients may be instructed to take only one-half of the normal first dose of an intermediate-acting insulin or a long-acting agent, followed by the full insulin dose at the next regularly scheduled time interval after the dental procedure. If patients are administering both intermediate and short-acting insulin, they may avoid the morning administration of the short-acting agent, administer one-half of the intermediate agent in the

morning and at the next meal, and return to the short-acting drug when normal oral intake is resumed. Supplementation with liquid or semisoft nutritional substances may be recommended to maintain a well-balanced diet.

Vasoconstrictor drugs should be included in local anesthetics to insure profound anesthesia. Excessive epinephrine should be avoided to prevent elevation of blood glucose levels. Local anesthetic should not contain more than 1:100,000 of epinephrine.^{6,7,126}

Antibiotic Use

Antibiotics are not necessary for routine dental procedures in diabetic individuals, but should be considered in the presence of overt oral infections and in conjunction with invasive periodontal or surgical procedures due to the potential for lower host resistance and delayed wound healing in diabetic patients. The need for antibiotics may vary depending on the state of the patient's metabolic control, but the choice of antibiotic, dosage, and route of administration is usually the same as for non-diabetic individuals. If tetracycline is indicated, some clinicians prefer doxycycline since it is not metabolized in the kidney where possible nephropathy or less severe kidney damage may have occurred. Glucocorticosteroids for control of post-surgical swelling should be avoided in diabetic patients since they can precipitate unwanted elevations of blood glucose.^{7,127}

MANAGEMENT OF MEDICAL EMERGENCIES IN THE PATIENT WITH DIABETES MELLITUS

In many cases, the person most knowledgeable in the control of blood glucose levels is the patient. The dental practitioner should briefly discuss with patients their recent history of blood glucose control. Also, the dental team should determine the location of any patient self-administered medication for diabetic emergencies prescribed by the physician. Patients should be encouraged to bring their self-monitoring blood glucose devices to the dental office and demonstrate its use to the dentist in case intra-operative glucose determination is required. Patients should be encouraged to communicate any perceived changes in their condition and assured that the dental team will support them as needed. Consults with the patient's physician might include a request for advice in managing the patient in a diabetic emergency.

The emergency most likely to occur in the dental office is hypoglycemia or insulin shock. Insulin shock may be precipitated in the IDDM patient by excessive exercise, stress, insulin overdose, or failure to maintain a proper dietary balance and occurs when blood glucose levels decrease to 40 mg/dl or lower. Signs and symptoms include mental confusion, sudden mood changes, and lethargy initially, followed by tachycardia, nausea, cold clammy skin, hunger, increased gastric motility, and increasingly bizarre

behavior. Hypotension, hypothermia, and loss of consciousness follow if the condition is not treated. In the most severe cases, seizures can develop with possible death. Signs develop rapidly, and treatment should be initiated as early as possible. Early treatment consists of administration of oral carbohydrates such as orange juice, soft drinks, or candy. If an intravenous line is in place, dextrose (10 to 20 ml of D50) can be administered intravenously. The patient usually responds within 5 to 10 minutes. In this event, the patient should be monitored until stabilized, and the patient's physician notified.^{6,7,126,127}

The emergency medical alert system should be activated if the patient fails to respond, and the patient should be transported to a hospital emergency room. Also, glucagon can be administered for the treatment of severe hypoglycemia, with the advantage that administration intravenously, intramuscularly, or subcutaneously is equally efficacious. Glucagon promotes glycogenolysis and gluconeogenesis, but the effect may be transient since the response is dependent on hepatic glycogen. Thus, unconscious patients should be given oral glucose when they regain consciousness to prevent recurrence of hypoglycemia. In addition, the practitioner should be aware that glucagon has cardiac inotropic effects.

Diabetic crisis (hyperglycemia) may develop when blood glucose goes over 200 mg/dl, with coma occurring at levels of 300 to 600 mg/dl. This condition develops slowly, and presents with characteristics similar to those found in the uncontrolled diabetic. In the later stages, the affected individual may become disoriented, with rapid and deep breathing and hot, dry skin. Acetone breath may be evident. Severe hypotension and loss of consciousness develop without proper treatment, so the conscious patient should be transferred to the hospital. The unconscious patient should be managed using basic life support procedures including airway maintenance and administration of 100% oxygen, followed by administration of intravenous fluids to prevent vascular collapse. Affected patients should not be given insulin prior to obtaining serum electrolyte and glucose values at the hospital. Recovery is usually slower than seen in patients with insulin shock.^{7,127}

It may not be possible to differentiate between hypo- and hyperglycemia in the disoriented or unconscious diabetic patient. In this case, treatment should be initiated for hypoglycemia, since hypoglycemic patients may deteriorate more rapidly to a life-threatening condition. Further, treatment for hypoglycemia or insulin shock with glucose will not significantly worsen the hyperglycemic state in the case of an incorrect diagnosis. Monitoring the patient's condition using a self-monitoring blood glucose device may differentiate between hypoglycemia and hyperglycemia, and may be useful in evaluating recovery from a hypoglycemic crisis.¹¹

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