Position Paper

Diabetes and Periodontal Diseases*

Erratum: The Position Paper on Diabetes and Periodontal Diseases published in the August 1999 issue of the *Journal of Periodontology* (1999;70:935-949) contained an erratum. The entire corrected paper is published below.

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. *J Periodontol 2000;71:664-678.*

Periodontal diseases often involve numerous and complex causes and symptoms. Reliance on this position paper in patient management will not guarantee a successful outcome. 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.

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: Type 1 (formerly insulin-dependent diabetes mellitus) and Type 2 (formerly non-insulin dependent diabetes). Diabetes insipidus results from a deficiency in the pituitary hormone vasopressin (anti-diuretic hormone), or from resistance to this hormone by the kidney. The decrease in production or action of vasopressin results in excessive urine production and polyuria, but does not have any effect on blood glucose levels.

Type 1 DM is caused by destruction of the insulin-producing ß cells of the pancreas. The pathophysiology may involve an autoimmune or virally mediated destructive process.[1-4] In theory, ß 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]

Type 2 DM 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. Type 2 DM patients are often obese and their glucose intolerance typically can be improved with control of diet and body weight. Additionally, agents to control glucose levels 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.[8,9] Type 2 DM constitutes 85 to 90% of diabetic cases, while Type 1 DM 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 diabetic cases. In contrast to the general population prevalence of 5%, the prevalence of Type 2 DM in individuals 65 years and older is 8.6%.[8,10,11] With improved screening and diagnostic tools, it can be expected that an increasing percentage of the population will be diagnosed with diabetes.

The American Diabetes Association has recently moved away from a classification system for diabetes that was based primarily on the type of pharmacological treatment used to manage the disease, and toward

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a system based on disease etiology.[12] The terms insulin-dependent and non-insulin dependent are no longer used. Likewise, the terms latent, subclinical, and chemical diabetes mellitus; prediabetes; potential diabetes; and adult-onset, maturity-onset, and juvenile-onset diabetes are outdated. Currently accepted diagnostic categories include: Type 1 DM; Type 2 DM; impaired glucose tolerance; impaired fasting glucose; gestational diabetes; and other specific types of diabetes such as those secondary to diseases of the pancreas, drug therapy, endocrinopathies, infections, and genetic disorders. Impaired glucose tolerance and impaired fasting glucose describe a metabolic stage intermediate between normal glucose homeostasis and diabetes.[12]

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 Type 1 DM, but occur to varying degrees in Type 2 DM. Weight loss may occur, especially in Type 1 DM. Nausea and vomiting may be seen in uncontrolled Type 1 DM and are associated with increasing ketoacidosis. Restlessness, irritability, and apathy may become evident.[7,13] 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. The "classic" complications of DM include retinopathy, nephropathy, neuropathy, macrovascular disease, and altered wound healing. 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.[7,13]

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 Type 2 DM by reducing the intake of refined sugars and high-fat foods, and by minimizing excess body fat.[14,15] Oral agents may be used for Type 2 DM. Sulfonylurea drugs stimulate insulin release from pancreatic ß cells and promote insulin uptake in body tissues. Short-acting sulfonylureas 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.[16] Repaglinide is a recently approved ultra-short-acting agent with a very rapid onset. Unlike sulfonylureas which are usually taken once or twice a day, repaglinide is taken immediately prior to each meal and has a decreased risk of hypoglycemia.[17] Other agents used to treat diabetes include metformin and troglitazone which act to increase tissue sensitivity to insulin without increasing release of insulin from the pancreas. Hypoglycemia is generally not associated with use of metformin or troglitazone.[17]

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 4 forms: a rapid-acting form with a duration of activity less than 5 hours (insulin lispro); short-acting forms with a 4- to 12-hour duration of activity (regular and semilente); intermediate-acting forms with an 18- to 20-hour duration of activity (isophane lente and NPH [neutral protamine Hagedorn]); and a long-acting form with a duration of activity of more than 30 hours (ultralente).[18] Modern insulin therapy often involves the use of a combination of rapid-, 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.[18] 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.[18] Use of human insulins has expanded rapidly since their advent and is more common than use of either bovine or porcine insulins. Experimental treatments for DM now under investigation include the use of immunosuppressive drugs, pancreas transplants, or transplantation of ß 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).[19] This multi-center study of 1,441 Type I DM patients compared complications in 2 cohorts; one using conventional insulin regimens (1 or 2 injections per day), and the other on a "tight control" regimen (3 or more daily injections or use of an insulin infusion pump). Over a 6.5 year period, the incidence of diabetic eye, kidney, and nerve complications was significantly reduced in the tight control cohort. For individuals with no evidence of pre-existing 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, Type 1 DM patients with periodontal treatment needs may be evaluated for risk of hypoglycemia during dental procedures based on their history and insulin regimen.

The recently completed United Kingdom Prospective Diabetes Study (UKPDS) has shown significant reductions in complications associated with Type 2 DM when control of blood glucose is improved.[20,21] Aggressive reduction of blood glucose using sulfonylureas, metformin, or insulin reduced the risk of retinopathy and nephropathy by 25% in this study of over 5,000 Type 2 DM patients. Because use of insulin or sulfonylureas increases the incidence of hypoglycemia, Type 2 DM patients on intensive treatment regimens may also have an increased risk of hypoglycemia during dental treatment.

Type 1 DM 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.[18]

Tests Used for Determining Blood Glucose Levels

The primary methods used to diagnose diabetes mellitus and monitor blood glucose levels have traditionally been fasting blood glucose, a combination of fasting blood glucose plus a 2-hour test after glucose loading (2-hour postprandial), and oral glucose tolerance tests (Table 1). New diagnostic guidelines allow use of a casual (non-fasting) plasma glucose for diagnosis and restrict routine use of the oral glucose tolerance test.[12] These tests clearly demonstrate the individual's capacity to regulate serum glucose levels. The casual plasma glucose test provides a simple screening tool since fasting is not required. Evaluation of urine glucose levels was used for many years as a screening and monitoring mechanism, but is insensitive and has been replaced by self-monitoring blood glucose instruments for patient self-assessment when feasible.[22] The glycated hemoglobin test (formerly called glycosylated hemoglobin) has been used as a monitoring tool, and has recently been advocated as a screening tool.[23] The glycated 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. Two different glycated hemoglobin

Table 1.
Diagnostic Criteria for Diabetes[12]

Diabetes mellitus may be diagnosed by any one of 3 methods. Whatever method is used must be confirmed on a subsequent day by using any 1 of the 3 methods.

1. Symptoms of diabetes plus casual (non-fasting) plasma glucose ≥200 mg/dl. Casual glucose may be drawn at any time of day without regard to time since the last meal. Classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss.
2. Fasting plasma glucose ≥126 mg/dl. Fasting is defined as no caloric intake for at least 8 hours.
3. Two-hour post-prandial glucose ≥200 mg/dl during an oral glucose tolerance test. The test should be performed using a glucose load containing the equivalent of 75 grams of anhydrous glucose dissolved in water. (This method is not recommended for routine clinical use.)

Categories of fasting plasma glucose (FPG) include:

1. FPG <110 mg/dl = normal fasting glucose
2. FPG ≥110 mg/dl and <126 mg/dl = Impaired fasting glucose
3. FPG ≥126 mg/dl = provisional diagnosis of diabetes (must be confirmed on subsequent day as described above)

Categories of 2-hour post-prandial glucose (2hPG) include:

1. 2hPG <140 mg/dl = normal glucose tolerance
2. 2hPG ≥140 mg/dl and <200 mg/dl = impaired glucose tolerance
3. 2hPG ≥200 mg/dl = provisional diagnosis of diabetes (must be confirmed on subsequent day as described above)

tests are available: the hemoglobin A1 (HbA1) test and the hemoglobin A1c (HbA1c) test. Each has a different range of normal values, with the normal HbA1 being less than about 8.0% and the normal HbA1c less than 6.0 to 6.5%.[18,23,24] Glycated hemoglobin values must be interpreted in the context of the range of normal values for the individual medical laboratory performing the service. Most recently, glycated albumin and glycated fructosamine have been developed as monitoring tools, although some evidence suggests that fructosamine may not be suitable for diabetes screening.[24] 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.[25,26]

Glucometers are commonly used by diabetic patients for home monitoring of their blood glucose levels using a single drop of blood from a finger stick. 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 diabetics.

In general, self-monitoring devices are not used to diagnose DM,[25] and their role in large-scale screening remains undecided. The American Diabetes Association recommends the devices for insulin-treated patients; pregnancy complicated by diabetes; and patients with unstable diabetes, a propensity to severe ketosis or hypoglycemia, prone to hypoglycemia who may not experience the usual warning symptoms, on intensive treatment programs, and with abnormal renal glucose thresholds.[21]

Quality control is essential for health care 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 DISEASES AND DIABETES

The criteria for diagnosing diabetes have undergone significant changes since the early 1960s. Likewise, the diagnosis of periodontal diseases has been better defined. Using refined standards for diagnosing these 2 disease states, several general trends are apparent. Uncontrolled or poorly controlled diabetes is associated with increased susceptibility to oral infections, including periodontitis.[27-31] The incidence of periodontitis increases among diabetic subjects after puberty and as the patient population ages.[32-44] Periodontal disease may be more frequent and severe in diabetic individuals with more advanced systemic complications.[39,42,45] The increased susceptibility does not correlate with increased levels of plaque and calculus.[33,44,46-48] Collectively, the evidence supports the theory that there is a relationship between the 2 diseases, especially in patients with poorly controlled diabetes mellitus or hyperglycemia.

Type 1 Diabetes Mellitus and Periodontal Diseases

In initial studies to investigate a relationship between periodontal disease and Type 1 DM, the periodontal status of 263 Type 1 DM patients was compared to 59 non-diabetic siblings and to 149 non-diabetic, unrelated controls.[35] No periodontal disease was found among the DM 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 DM 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 Type 1 DM 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. In a study of 71 Type 1 DM patients with a 16.5 year mean duration of disease, the patients were divided into poorly controlled and well controlled based on long-term medical records.[49] Under similar conditions of plaque control, adult subjects with poorly controlled diabetes had lost more approximal attachment and bone than well-controlled diabetic subjects.

Table 2.

Quality Control for Using Self-Monitoring Blood Glucose Devices in the Outpatient Setting[25]

- 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.

Type 2 Diabetes Mellitus and Periodontal Diseases

Epidemiologic studies have been done on Pima Indians, a population suffering from an extremely high prevalence of Type 2 DM. In the initial study of periodontal disease in this community, a cross-sectional analysis was done using periodontal attachment loss and radiographic bone loss.[50] 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 (6 Ramfjord index teeth), giving a subset of 1,342 individuals.[10] Compared to non-diabetic individuals, subjects with Type 2 DM 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, gender, or hygiene. When prevalence of clinical attachment loss (1 or more sites ≥5 mm) was evaluated by age, diabetic subjects aged 15 to 24 had 4.8 times more periodontal disease than non-diabetic subjects, while those aged 25 to 34 had 2.3 times more periodontal disease. The prevalence of periodontal disease in the 3 remaining age groups was marginally higher among diabetic subjects: for diabetic patients aged 35 to 44, the ratio was 1:5; for those aged 45 to 54 and age >55, the ratio was 1:1. The decreased ratio between diabetic and non-diabetic subjects in the older age groups was primarily due to the high prevalence of periodontal disease in non-diabetic Pima Indians (≥75% 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.[51] 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.[51] In a 2-year longitudinal study, Type 2 DM subjects had a significantly increased risk of progressive alveolar bone loss compared to non-diabetic subjects, with an odds ratio of 4.2.[52] The increased risk of advancing bone loss was greatest among younger individuals. In addition, compared to non-diabetic controls, DM patients with poor glycemic control had a much greater risk of progressive bone loss (odds ratio = 11.4) than did well-controlled subjects (odds ratio = 2.2).

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.[50,53] A Finnish study corroborated these findings; more attachment loss and approximal bone loss were found in poorly controlled than well-controlled Type 1 DM subjects.[49]

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.[33,54] This correlation with the duration of diabetes is similar to that of other complications of diabetes such as nephropathy, retinopathy, neuropathy, and vascular disease.

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.[45] 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.[55] 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.[56] 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.[53]

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."[57] 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.[40,56,58] Diabetic children were found to have significantly more gingival inflammation than children without diabetes with no difference in plaque scores between the 2 groups.[37] Diabetic children with poor metabolic control had significantly higher gingival index scores than did non-diabetic controls.[59]

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.[60-63] Increased glucose content also has been demonstrated in gingival crevicular fluid.[64,65] 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.[66] In addition, many diabetic subjects take medications that induce oral dryness which can contribute to the xerostomic state.[46,67,68] 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.[69]

An increased incidence of dental caries has been found in association with uncontrolled or poorly controlled diabetes in both humans and experimental animals.[39,70-72] 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.[46,67,73,74]

FACTORS POTENTIALLY CONTRIBUTING TO DEVELOPMENT OF PERIODONTAL DISEASE

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,[75-79] adherence,[80] and phagocytosis.[79,81-84] Studies of PMN defects suggest that this dysfunction could lead to impaired host resistance to infection.[68,85,86]

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.[87,88] 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.[89] 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.[88]

PMN defects have been studied in rats chemically treated to induce diabetes.[90] Chemotactic agents, FMLP, and casein were applied atraumatically on the gingival margin of rats with chemically induced diabetes and non-diabetic controls. Diabetes at 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 and Advanced Glycation Endproducts

Synthesis, maturation, and homeostasis of collagen appear to be affected by glucose levels. Studies of skin fibroblasts have shown that hyperglycemic conditions have reduced cell proliferation and growth[91,92] and reduced synthesis of both collagen[91,93,94] and glycosaminoglycan.[95] In addition, gingival fibroblasts from diabetic patients synthesize less collagen compared to non-diabetic subjects.[96] Rats with experimentally induced diabetes have impaired production of bone matrix components by osteoblasts and decreased collagen synthesis by gingival and periodontal ligament fibroblasts.[97-99] Tetracycline was found to ameliorate the suppressed metabolic activity of osteoblasts and periodontal ligament fibroblasts of diabetic rats.[99]

In addition to finding decreased collagen production in association with diabetes, investigators also have found increased collagenase activity in gingival tissue in animals.[97-99] Crevicular fluid collagenolytic activity also was increased in diabetic patients;[100] 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.[101] Collectively, these results indicate that the increased collagenase was endogenously derived independently of bacterial factors. Interestingly, the increased crevicular fluid collagenase levels found in patients with diabetes can be inhibited in vitro by tetracycline.[100]

In a hyperglycemic environment, numerous proteins including collagen undergo a non-enzymatic glycosylation process to form advanced glycation endproducts (AGE). The formation of AGE plays a

central role in diabetic complications.[102] AGEs accumulate with chronic hyperglycemia. AGE formation alters the function of numerous extracellular matrix components, modifying matrix-matrix and cell-matrix interactions. These alterations have an adverse effect on target tissues, especially collagen stability and vascular integrity. AGE formation on collagen results in increased cross-linking between collagen molecules. This cross-linking of collagen significantly contributes to reduced solubility and decreases turnover rate.[94,103-105] 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.[98,106]

Monocytes, macrophages, and endothelial cells possess high-affinity receptors for AGEs.[102,107,108] AGE binding to macrophage and monocyte receptors may induce a hyperresponsive cellular state resulting in increased secretion of interleukin (IL)-1, insulin-like growth factor, and tumor necrosis factor (TNF)-α, while endothelial cell binding results in procoagulatory changes leading to focal thrombosis and vasoconstriction.[102,107,108] Monocytes from patients with diabetes produce significantly greater amounts of TNF-α, IL-1ß, and PGE_2 in vitro than do non-diabetic controls.[109,110] Clinically, diabetic subjects with periodontitis have significantly higher gingival crevicular fluid levels of both IL-1ß and PGE_2 compared to non-diabetic controls matched for periodontal disease severity.[110] AGE-mediated events are of primary importance in the pathogenesis of diabetic complications such as retinopathy, nephropathy, neuropathy, and atherosclerosis. They may also be involved in tissue changes within the periodontium, rendering the diabetic patient with poor glycemic control and elevated AGE production susceptible to increased tissue destruction.[111]

AGE formation results in production of reactive oxygen intermediates. AGEs have been detected in gingival tissues of diabetic patients and have been shown to increase oxidant stress in these tissues when compared to non-diabetic individuals.[111] This enhanced oxidant stress may be responsible for the vascular injury common to diabetic complications.

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 PMN) from diabetic subjects show that these individuals may have impaired defense mechanisms.[75-86] As previously stated, studies of PMN from diabetic animals (streptozotocin-induced) show that insulin therapy can reverse the defective function of these cells.[90]

Insulin resistance is a condition that exists during acute infections.[112-115] This condition occurs independently 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.[116,117] The molecular basis for infection-induced insulin resistance is not clearly understood.

Vascular changes are common in patients with diabetes.[118] Basement membrane (BM) proteins become glycosylated in a hyperglycemic environment, with thickening and changes in the physical properties.[103,118,119] Gingival capillaries of diabetic subjects have thickened BM,[120-122] 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.[123]

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.[93,124]

The late inflammatory response to wound healing has been found to be altered in diabetes.[125] Wound chambers in normal and streptozotocin-induced diabetic mice showed marked differences in both cellular infiltration (PMN) and cytokine levels (TNF and IL-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 IL-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.[126] 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.[127] An association between reduced mitogenic activity and decreased wound strength has not been determined, but may 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.[128] 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.[119]

In one study, *Capnocytophaga* species predominated in periodontal lesions of young Type 1 DM patients, averaging 24% of the cultivable flora.[129] *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 Type 1 DM patients.[119,129-131]

The composition of the periodontal microflora found in periodontally diseased sites of Type 2 DM 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 Type 2 DM patients.[130] 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 Type 2 DM subjects. Higher levels of *Prevotella intermedia* have been reported in diseased versus healthy periodontal sites in Type 1 DM.[119] The occurrence of *A. actinomycetemcomitans* and *Porphyromonas gingivalis* was similar to that found in chronic adult periodontitis. No significant differences in the subgingival microbiota were found between Type 1 diabetic children and their non-diabetic siblings.[132]

DENTAL THERAPY

General Considerations

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 may 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.[116,117,133-136] On occasion, oral infections may even be life-threatening to diabetic patients.[31,137,138]

The presence of periodontal disease may aggravate glycemic control. In a longitudinal study, Type 2 DM subjects with severe periodontal disease at baseline demonstrated significantly worse glycemic control than diabetic subjects with minimal periodontal destruction.[139] The presence of severe periodontal infection may also increase the risk for microvascular and macrovascular diabetic complications. A case-control study examined diabetic complications in 39 diabetic patients with severe periodontitis compared with 39 diabetic patients with only gingivitis or mild periodontitis.[140] Over a 1- to 11-year follow-up period, diabetic subjects with severe periodontal disease at baseline had a significantly greater prevalence of proteinuria and a greater number of cardiovascular complications including stroke, transient ischemic attack,

angina, myocardial infarction, heart failure, and intermittent claudication than did diabetic patients with minimal periodontal disease.

Several studies, including controlled clinical trials, have shown that control of periodontal infection through mechanical therapy combined with systemic tetracycline antibiotics may improve glycemic control.[133,135,136] As periodontal inflammation decreased and clinical parameters improved, glycated hemoglobin values decreased to a statistically and clinically significant degree.[135,136] This positive effect may be most pronounced in poorly controlled diabetic patients with relatively severe periodontitis. Insulin requirements may also be reduced in some Type 1 DM patients following periodontal treatment.[134,141] One study in which scaling and root planing was performed without adjunctive use of systemic antibiotics showed no significant effect on glycemic control.[142]

The short-term response of well-controlled diabetic subjects to non-surgical periodontal therapy appears equivalent to that of non-diabetic individuals.[143,144] Similar improvements in probing depths, attachment levels, and subgingival microbiota have been demonstrated.[144] While most diabetic patients may show improvement in clinical parameters of disease immediately after therapy, poorly controlled patients have a more rapid recurrence of deep pockets and a less favorable long-term response.[145] Five years after a combination of non-surgical and surgical periodontal treatment with regular supportive periodontal therapy, diabetic patients had a similar prevalence of sites demonstrating gain, loss, or no change in clinical attachment.[146] Most of the diabetic subjects in this study had well- or moderately controlled glycemia as determined by glycated hemoglobin levels.

Timing of Treatment

Patients with well-controlled DM can be treated similarly to non-diabetic patients for most routine dental needs. Procedures should be short, atraumatic, and as stress-free as possible. Appropriate vasoconstrictor agents may be included in local anesthetics to insure profound anesthesia.

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 often preferred because levels of endogenous corticosteroids are generally higher at that time and stressful procedures may 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.

For many dental procedures, no change in insulin regimen or oral agents is necessary. For long or stressful procedures, patients may alter their usual drug regimen in consultation with their physician. Type 2 DM patients may reduce or omit oral hypoglycemic medications on the day of the procedure followed by a return to normal dosage the following day. For patients taking insulin, changes in the timing, amount, or type of insulin injected may be warranted.[18,24] On the day of the procedure, the patient may reduce or eliminate the dose of insulin taken prior to the procedure. Assuming a normal diet would be resumed following treatment, the patient may take the usual insulin dose at the next regularly scheduled time interval after the dental procedure. If the patient is unable to resume a normal diet after dental treatment, longer-term alterations in insulin or oral agents may be needed. Diet supplementation with liquid or semisoft nutritional substances may also be useful.

It is important for the periodontist to know the medication and diet regimen being used by the patient. For many patients, periodontal treatment can be timed appropriately during the day to avoid peak insulin activity. In many cases, especially in patients taking multiple injections of insulin daily, periodontal treatment may occur at a time coinciding with peak insulin activity. The periodontist must be aware of the risk for hypoglycemia during the dental appointment and be ready to manage such an occurrence.[18]

Antibiotic Use

Antibiotics are not necessary for routine dental procedures in diabetic individuals, but may be considered in the presence of overt oral infections due to the potential for lower host resistance and delayed wound healing in diabetic patients.[26] The need for antibiotics may vary depending on the patient's metabolic control, but the choice of antibiotic, dosage, and route of administration is usually the same as for non-diabetic individuals. The combination of mechanical debridement and systemic tetracycline may provide a greater positive effect on glycemic control in some DM patients compared to mechanical debridement alone.[133-136,142] 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.

MANAGEMENT OF MEDICAL EMERGENCIES

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 may want to bring their self-monitoring blood glucose devices to the dental office in case intraoperative glucose determination is required. Patients should be encouraged to communicate any perceived changes in their condition to the dental team. 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 insulin-using diabetic patient by excessive exercise, stress, insulin overdose, or failure to maintain a proper dietary balance. While signs and symptoms of hypoglycemia do not usually occur until blood glucose levels fall below 60 mg/dl or lower, symptoms may occur at higher levels in patients whose usual blood glucose concentration is markedly elevated (poor glycemic control) and falls rapidly.[18] Pretreatment determination of blood glucose levels using the patient's glucometer may aid in prevention of hypoglycemia. Individuals with glucose levels near or below the lower end of the normal range before treatment (about 70 to 80 mg/dl) may benefit from consuming a small amount of oral carbohydrate prior to therapy. Signs and symptoms of hypoglycemia initially include mental confusion, sudden mood changes, and lethargy, followed by tachycardia, nausea, cold clammy skin, hunger, increased gastric motility, and increasingly bizarre behavior. Hypotension, hypothermia, and loss of consciousness may 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 at least 15 grams of oral carbohydrates such as orange juice, soft drinks, or candy.[18] 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.[7,18,147] 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 may develop when blood glucose levels over 200 mg/dl are present for an extended period of time. Hyperglycemic crisis, which develops slowly and generally requires prolonged periods of hyperglycemia, is much less common in the dental office than hypoglycemic emergency. In the Type 1 DM patient, diabetic ketoacidosis may occur.[18] It presents with characteristics similar to those found in the uncontrolled diabetic. In the later stages, as acidosis develops, the affected individual may become disoriented, with rapid and deep breathing and hot, dry skin. Acetone breath may be evident. While the Type 2 DM patient is resistant to ketoacidosis, prolonged hyperglycemia may cause hyperosmolar non-ketotic diabetic acidosis.[18] In this condition, acidosis occurs in the absence of blood ketones. In both ketoacidosis and hyperosmolar non-ketotic acidosis, severe hypotension and loss of consciousness develop without proper treatment, so the conscious patient should be transferred to the hospital.[18] 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.[7,147]

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 glucometer may differentiate between hypoglycemia and hyperglycemia, and may be useful in evaluating recovery from a hypoglycemic crisis.[18]

SUMMARY

Diabetes mellitus has significant impact on tissues throughout the body, including the oral cavity. Research indicates that diabetes, especially when poorly controlled, increases the risk of periodontitis. While the exact mechanisms have not been clearly established, alterations in host defenses and normal tissue homeostasis appear to play a major role. Evidence also suggests that periodontal infection and periodontal treatment have the potential to alter glycemic control. Further research is required to delineate more precisely the pathways through which diabetes and periodontal disease interact.

Advances in medical management of diabetes require a heightened awareness by the periodontist of the various treatment regimens used by diabetic patients. Intensive medical treatment with oral agents and insulin promises to decrease the long-term risks of major complications of diabetes; however, these treatments increase the risk of medical emergencies in the dental office, especially hypoglycemia. Familiarity with the various medications, monitoring equipment, and devices used by diabetic patients allows provision of appropriate periodontal therapy while minimizing the risk of complications.

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