Diabetes Mellitus as a Modulating Factor of Endodontic Infections

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Abstract: Diabetes mellitus is a chronic disease with serious health consequences. The association between diabetes and periodontal disease is well documented. However, the progression and healing of endodontic infections in diabetic patients has not been adequately studied. In this review, diabetes mellitus is explored as a potential modulating factor of endodontic pathosis. Recent data on the relationship between the clinical presentation of pulpal and periradicular disease, as well as the outcome of endodontic treatment in diabetic and nondiabetic patients, are presented. Diabetics who present for endodontic treatment, particularly those with periradicular pathosis, may have increased perioperative symptoms. Cases with preoperative periradicular lesions are less likely to be determined successful two years or longer postoperatively if the patient reports a history of diabetes. Studies examining the pathogenesis of periradicular lesions in mouse models with uncontrolled type 1 diabetes suggest that the lesion size may be increased and the animals have increased serious sequelae. Preliminary findings suggest that some bacterial species may be more prevalent in necrotic pulp of diabetic than nondiabetic patients. More studies are needed to further explore the microbiology of endodontic infections and to determine effective treatment strategies in both diabetic and nondiabetic patients.

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Diabetes mellitus is a chronic disease with serious long-term debilitating complications and no known cure. The relationship between oral health and diabetes has been extensively studied, particularly with respect to periodontal disease and, to a lesser extent, dental caries. Endodontic infections are very prevalent and are caused by microbial factors that are very similar to those that cause periodontal disease. However, the literature on the pathogenesis, progression, and healing of endodontic pathosis in diabetic patients is remarkably scarce.

In this review, the epidemiology and pathogenesis of periradicular infections will be briefly described. The literature addressing the natural history of endodontic infections and endodontic treatment outcome in diabetics will be discussed. Finally, recent data on the microbiology and host response in periradicular infections of diabetic and nondiabetic hosts will be presented.

Epidemiology and Pathogenesis of Periradicular Lesions

Periradicular (PR) lesions result from irritation of the PR tissues by polymicrobial irritants from root canals, in teeth with necrotic pulps. The prevalence of PR lesions in the general population of the United States has not been established. However, estimates based on prevalence in other countries and prevalence among dental clinic populations in this country show that the percentage of individuals with PR lesions in at least one tooth is 41-47 percent. This prevalence tends to increase to 60-72 percent in older patients.

In dental patient populations, the percentage of teeth with PR lesions has been estimated to range
from 3 to 5 percent of all teeth examined. However, among teeth that have been endodontically treated, the percentage with PR lesions is 31-61 percent. PR lesions are, therefore, quite prevalent, especially in relation to endodontically treated teeth.

A significant clinical complication of PR disease is acute exacerbation, which results in significant pain that may be associated with localized or spreading swelling. This dento-alveolar infection causes significant pain and suffering for patients and, occasionally, can cause significant morbidity or rarely even mortality. Exact estimates of the likelihood of acute exacerbation or its serious sequelae are not available. According to the American Dental Association’s 2000 Survey of Dental Practice, about 10 percent of annual visits in general dental practitioners’ offices are “walk-in and emergency visits.” The percentage of dental emergencies is probably much higher among patients of dental schools and hospital-based dental clinics. It has been shown from mail or phone surveys that 12-14 percent of the North American population has acute toothache at any given time. Some of these cases involve painful pulpitis rather than painful PR lesions. The incidence of painful pulpitis and painful apical periodontitis in emergency dental patients has been estimated to be 35 percent and 31 percent respectively. Moreover, some cases present as asymptomatic or mildly painful PR lesions, but the patients experience flare-ups after initial root canal instrumentation, requiring unscheduled emergency visits. It has been reported that interappointment flare-ups occur in 2-4 percent of all endodontic cases.

Another important complication of PR lesions is resistance to therapy. Endodontic prognosis studies have shown that success rates of teeth with preoperative lesions range from 68 to 86 percent. These and other prognosis studies demonstrate that the presence of a preoperative lesion lowers the chances of long-term success compared with cases with vital pulp, where a successful outcome occurs in more than 90 percent of cases. While the reasons for these less successful outcomes are not fully understood, it is thought to be primarily due to the difficulty of total elimination of microorganisms from the root canal system, and possibly the dentinal tubules, in cases with endodontic infections.

Pulpal and Periradicular Disease in Diabetic Patients

About 17 million people in the United States (6.2 percent of the population) have diabetes. Close to one third of these individuals (5.9 million or 2.2 percent) are undiagnosed, mostly type 2, diabetics. Minorities have increased prevalence of diabetes; it is estimated that 13 percent of non-Hispanic blacks, 10 percent of Hispanic/Latino Americans, and 15 percent of American Indians and Alaska Natives receiving care from the Indian Health Service have diabetes. Type 1 diabetes represents about 5-10 percent of all diagnosed cases, or about 0.5-1 million patients.

About 1 million new cases of diabetes are diagnosed every year, and in 1999 about 450,000 deaths occurred among people with diabetes aged twenty-five years or older. Of those individuals, 68,399 had diabetes noted as the underlying cause of death, making diabetes the sixth leading cause of death in the United States.
There are numerous reports documenting, quite convincingly, that diabetes mellitus (DM), especially when poorly controlled, is associated with significant periodontal disease and tooth loss due to periodontal disease. However, in patients with DM, very little data are available on the pathophysiology and clinical progression of PR lesions or the prognosis of endodontic treatment. An earlier report proposed that healing of periapical lesions will not occur if diabetes is not controlled and that the lesions will increase in size despite endodontic treatment. In a Swedish subpopulation, female residents with long-duration insulin-dependant DM (IDDM) were found to have an increased prevalence of endodontically treated teeth with PA lesions than residents with short-duration IDDM or age- and sex-matched nondiabetics. This difference was statistically significant in all individuals with more than one PR lesion. In an earlier clinical study, radiographic healing of PR lesions following endodontic treatment was closely monitored in twelve patients with low plasma glucose (70-89 mg/dL) and thirteen patients with high glucose (90-110 mg/dL). None of the patients in either group was a known diabetic. At the endodontic treatment visit, blood glucose measurement was done two hours postprandially. After thirty weeks, the PR radiolucencies in the low glucose groups were reduced by an average of 74 percent compared with a reduction of only 48 percent for the high glucose group. Another study reported that patients with DM had a disproportionately high percentage of clinically severe pulpal or periodontal infections (24 percent of all cases), but had a much lower percentage of moderate infections (2.3 percent). Taken together, these reports provide preliminary findings that suggest some differences in the natural history of endodontic infections in the diabetic patient. Clearly, larger scale studies performed with a more objective design are needed to test the hypotheses presented.

### Outcome of Endodontic Treatment in Diabetic and Nondiabetic Patients

Since the mid-1990s, the Department of Endodontontology of the University of Connecticut Health Center has developed and used an Endodontic Electronic Record (EER) system. This is a secured client/server database system that allows chairside entry of medical history and endodontic diagnosis and treatment data of all predoctoral and postgraduate student patients. The system also organizes endodontic follow-up examinations and contains data on treatment outcome for those cases where the patients did return for follow-up examination.

The percentage of new endodontic patients who reported that they have diabetes in the last six years is shown in Figure 1. These figures are close to 4 percent, which is the percentage of known diabetics in the general population (6.2-2.2 percent, as noted before). In the patient cohort studied, diabetics represented 4.6 percent of all patients, but had 5.2 percent of the endodontic cases.

Data on nonsurgical endodontic cases entered from 1995 for predoctoral students and 1997 for postgraduate students through October 2001 were analyzed with respect to variables on clinical presentation, diagnosis, flare-up rates, and treatment outcome in diabetic and nondiabetic patients. Treatment outcome was restricted to cases that have been followed up for two years or longer after obturation, including all cases that failed at any time. The sample consisted of data on 7,516 endodontic cases (5,244 patients) that presented for endodontic assessment and/or treatment, including 394 cases from 242 diabetic patients (fifty-eight of whom were on insulin). For diabetic patients, the designation of type 1 or type 2 was not used on older cases, since this classification is relatively new, so reference was made only as to whether the diabetic patients were managed with insulin. Of the whole cohort, 5,494 cases had endodontic treatment completed, and the rest did not need treatment or had treatment started but not completed.

An examination of all presenting patients revealed that, in patients diagnosed with PR lesions, diabetic patients on insulin tended to have a higher incidence of PR pain compared with the non-insulin dependant diabetics or the nondiabetic patients (Chi-square; p=0.058). Diabetics in general also had about twice the rate of flare-ups compared to nondiabetics (4.8 percent vs. 2.3 percent, Chi-square; p=0.09). No differences were found between diabetics and nondiabetics with PR lesions in the presence of sinus tracts, swelling, or the size of the PR lesion as noted by the providers.

In cases that were followed up after obturation, success was generally defined as the lack of any signs and symptoms and the complete radiographic healing of PR lesions. Cases with no signs and symptoms that had reduction but incomplete healing of

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the lesions were classified as uncertain; any other cases were classified as failing. Only 540 cases (including seventy-three cases from diabetic patients) had follow-up data longer than two years postoperatively. These cases, which represented about 10 percent of the initial sample, included all cases determined to have failed at any time. Using univariate analysis, the following individual factors were found to significantly affect the treatment outcome in the total recall sample: presence of preoperative PR lesion, presence of a permanent restoration at the time of follow-up examination, length of time to recall, primary treatment vs. nonsurgical retreatment, treatment provider (predoctoral vs. postgraduate student) and the age of the patient. Diabetes did not affect the treatment outcome in the total sample. However, when only cases with preoperative PR lesions were considered (174 cases including sixteen from diabetic patients), diabetics had a much lower percentage of successful cases compared with nondiabetics. Therefore, a hierarchical logistic regression analysis was performed on cases with preoperative lesions, which considered all the significant factors mentioned previously in addition to the gender of the patient. The results showed that diabetics with preoperative PR lesions had a significantly lower chance of successful outcome at two years or longer postoperatively compared with nondiabetics (p<0.001). There were many uncertain cases in this study, and since a large sample of patients with longer follow-up periods of three or four years was not available, it is not known whether diabetes prevents or merely delays the healing process of preoperative PR lesions. We are currently working on analyzing the outcome after longer evaluation periods and with larger groups of patients.

Pathogenesis of Periradicular Lesions in Type 1 Diabetic Animal Models

Animal models allow the testing of the specific hypotheses with fewer confounding variables than can be tested in clinical studies. The pathogenesis of PR lesions can be studied in relation to standardized amounts and types of irritants, and could be examined radiographically, histologically, and histomorphometrically. Moreover, the expression of certain inflammatory mediators can be examined at the mRNA or the protein levels.
There are a number of different rodent models for diabetes, particularly type 1 diabetes. Two models are commonly used: Streptozotocin-induced diabetes in rats and non-obese diabetic (NOD) mice. The advantages of the Streptozotocin model is that diabetes can be induced in a controlled manner in all animals and the animals in the diabetes and nondiabetes groups are of same genetic background. However, Streptozotocin, which is selectively cytotoxic to the islet cells in the pancreas, may also be cytotoxic to other tissues such as the liver and kidneys. Using Streptozotocin-induced hyperglycemic rats, Kohsaka et al.51 demonstrated that induced PR lesions were larger in size than in nondiabetic controls. No significant infections or mortality among the animals were reported.

The NOD mouse is a closer model to human type 1 DM.52 About 40-70 percent of these animals (more so in females) spontaneously develop autoimmune DM, marked by glucosuria, insulitis, and weight loss. Diabetes onset is marked by increase in autoantibodies to insulin and glutamic acid dehydrogenase (GAD).53

We compared the pathogenesis of PR lesions in diabetic NOD and nondiabetic BALB/c mice.54 In this study, lesions were induced by two methods. Either the pulp was exposed to the oral cavity for two or five weeks, or the exposures were inoculated with three endodontic bacterial pathogens: Fusobacterium nucleatum, Peptostreptococcus micros, and Streptococcus intermedius, for one or five weeks. The inoculated groups were intended to simulate a virulent endodontic infection, where the one-week group was sealed with a dentin bonding agent and the five-week group received reinoculation every other week.

Significantly more NOD mice expired prematurely as a result of PR lesion induction compared with nondiabetic controls, particularly in the one-week sealed inoculations group. Furthermore, among the animals that survived to their predetermined time points, NOD mice with pulp exposures lost significantly more weight than unexposed control NOD mice, indicating increased morbidity. Histomorphometric and immunohistochemical analyses were performed of the PR lesions of the animals that survived to their predetermined time points to determine the lesion size and expression of the bone-modulating cytokine interleukin-6 (IL-6). These analyses did not reveal any differences between the diabetic and nondiabetic animals. Similar analyses among the animals that expired could not be performed.

These studies suggest that the type 1 diabetic host, with no glycemic control, may experience an increase in PR lesion size, as well as in morbidity and mortality in response to endodontic pathogens.

In the latter study, one more experiment was performed on the five-week exposed mouse molars that were inoculated with bacteria to explore the relative difference in sensitivity of anaerobic culturing and molecular identification techniques. The results showed that, in the case of the two strict anaerobes used, F. nucleatum and P. micros, identification of the bacteria using polymerase chain reaction (PCR)-based methods was significantly more sensitive than culture-based methods.54

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**Microbiological Findings in Endodontic Infections of Diabetic and Nondiabetic Patients**

One hypothesis that may explain why the diabetic host may be more susceptible to significant infections is the presence of different root canal microbial profiles in teeth with pulp necrosis and that diabetics harbor a more virulent microbial profile. A number of studies have compared the bacterial flora associated with periodontal disease in diabetic and nondiabetic patients with no conclusive findings. For example, when sulcular flora from children and adolescents with type 1 DM was compared with that from their nondiabetic siblings, there were no significant differences.55 However, when these same groups were followed for three years, there was a statistically significant increase in P. intermedia in patients with DM at the deepest probing sites.56 Also, significantly more P. gingivalis was recovered from insulin-dependent diabetic patients.57 In these studies, no other significant differences between putative periodontal pathogens or correlation to the level of metabolic control were found.58 Only traditional culturing methods were used, with their classic limitations in these studies. The use of the more sensitive technique of PCR amplification of 16S rDNA may reveal differences in the flora of diabetic and nondiabetic patients.

The differences in treatment outcome that we have previously observed in cases with PR lesions and the trend toward increased apical symptoms or interappointment flare-ups may be related to the pres-
ence of more virulent microorganisms in root canals with necrotic pulp of diabetic patients. It is known, for example, that diabetic patients have increased oral candidiasis and are more likely to have the symptomatic variant of this disease. We have started conducting studies on molecular identification of root canal microorganisms in endodontic infections of diabetic and nondiabetic patients. We have elected to use molecular methods because of their increased sensitivity compared with culturing methods as noted before. In a recent study, we sought to identify ten putative endodontic pathogens from symptomatic and asymptomatic, diabetic and nondiabetic patients with pulp necrosis and PR lesions. Microbial samples were collected aseptically from necrotic pulp of twenty-four patients including six diabetics undergoing endodontic treatment. DNA was extracted from the specimens and subjected to PCR amplification with universal bacterial primers for the 16S rRNA gene, as well as primers specific to the organisms listed in Table 1. The results showed that *F. nucleatum*, *P. micros*, and *Streptococcus* spp. were the most prevalent of the microorganisms examined. There were highly significant associations between *Streptococcus* spp., Odds Ratio (OR)=13, p<0.001, and the combination of *Streptococcus* spp. and *F. nucleatum* (OR=11, p=0.01) and preoperative pain. With respect to diabetes, there was a positive, yet nonsignificant, association between diabetes and the presence of *P. endodontalis* (OR=4) and *P. gingivalis* (OR=3.4). The number of different microorganisms detected per specimen was, on average, higher in the diabetic vs. nondiabetic specimens, but the differences were not statistically significant.

In another study, we have analyzed these microbial specimens for the presence of another virulent endodontic bacterial pathogen, *Eubacterium* spp. Primers that are specific for several species of *Eubacterium*, but negative with other closely related organisms, were used to amplify extracted DNA. The resulting amplicons were directly sequenced using the amplification primers and then phylogenetically analyzed to reveal the identity of the individual *Eubacterium* species detected. The results revealed that sixteen of twenty-two specimens (73 percent) were positive for *Eubacterium* spp. Of those, nine (56 percent) were matched to *E. infirmum*, an organism that has been detected in periodontal disease, but has not been previously reported in endodontic infections. The association between the presence of *E. infirmum* and diabetes was found to be statistically significant (OR=9.6; p=0.04). Taken together, these two studies provide some preliminary data on the potential increased prevalence of some virulent endodontic pathogens in root canals of diabetic patients. Larger studies are currently under way to ascertain if these or other associations are consistent.

### Summary and Future Directions

Endodontic infections lead to periradicular pathosis, which is mostly asymptomatic and is remarkably prevalent. Increased PR disease severity is manifested clinically by increased size of PR radiolucency,

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Percent of Positive Specimens</th>
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<tbody>
<tr>
<td>Universal bacterial 16S rRNA gene</td>
<td>Diabetic Patients (n=5)</td>
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<tr>
<td></td>
<td>Nondiabetic Patients (n=17)</td>
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<tr>
<td></td>
<td>Total Positive Specimens (n=22)</td>
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<tr>
<td><em>Fusobacterium nucleatum</em></td>
<td>100 percent</td>
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<tr>
<td><em>Peptostreptococcus micros</em></td>
<td>40 percent</td>
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<tr>
<td><em>Streptococcus</em> spp.</td>
<td>40 percent</td>
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<tr>
<td><em>Prevotella nigrescens</em></td>
<td>20 percent</td>
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<tr>
<td><em>Porphyromonas endodontalis</em></td>
<td>40 percent</td>
</tr>
<tr>
<td><em>Bacteroides forsythus</em></td>
<td>20 percent</td>
</tr>
<tr>
<td><em>Enterococcus</em> spp.</td>
<td>0 percent</td>
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<tr>
<td><em>Treponema denticola</em></td>
<td>20 percent</td>
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<tr>
<td><em>Porphyromonas gingivalis</em></td>
<td>20 percent</td>
</tr>
<tr>
<td><em>Prevotella intermedia</em></td>
<td>0 percent</td>
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associated symptoms of pain or swelling, or resistance to treatment.

The information available on the pathogenesis, progression, and healing of pulpal and periradicular pathosis in diabetic patients remains in its infancy. Many clinical studies that have examined factors affecting the prognosis of endodontic therapy have either not reported on the medical history of patients or have eliminated patients with compromised medical histories, such as diabetics, to minimize variables. This problem may have been due to the difficulty in controlling for the degree of glycemic control of diabetic patients or the difficulty in including patients who have not received additional precautionary treatment, such as antibiotic therapy or tooth extraction, which would not otherwise be done.

In this review, data was presented to show the association between preoperative PR lesions in diabetics and a reduced therapeutic success at two years or longer postoperatively, compared with nondiabetics. Animal studies show that the induction of PR lesions in uncontrolled type 1 diabetic rodent models is associated with increased lesion size or morbidity and mortality. Finally, preliminary data reveal some associations between the presence of diabetes and increased findings of certain pathogenic microorganisms in root canals with necrotic pulp.

A number of important unanswered questions should be addressed in future research in this area. More treatment outcome studies that utilize larger patient databases, preferably in multiple centers, should be performed. The glycemic control of the patients should be studied as to whether it affects the treatment outcome. Furthermore, the differences between type 1 and type 2 diabetics should be explored. Diabetic patients, particularly older type 2 diabetics, have a number of concomitant medical conditions that have to be carefully assessed when performing these studies. The concomitant use of antibiotics or antifungal agents for oral or nonoral complications of an odontogenic abscess: mediastinitis, thoracic empyema and cardiac tamponade. J Oral Maxillofac Surg 1995;73:69-74.

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REFERENCES