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Diabetes in the Pathogenesis of Periapical Lesions

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ABSTRACT

Background: Diabetes mellitus is a chronic metabolic disorder associated with impaired wound healing and increased susceptibility to infections. Its impact on the development and severity of periapical lesions is clinically significant due to altered immune response and inflammatory profiles.

Objective: To investigate the relationship between diabetes mellitus and the pathogenesis of periapical lesions and compare lesion characteristics between diabetic and non-diabetic patients.

Methods: A comparative cross-sectional study was conducted involving 100 patients divided into diabetic (n=50) and non-diabetic (n=50) groups. Diabetic status was confirmed using HbA1c ≥6.5%. Periapical lesions were evaluated using digital radiographs and graded by the Periapical Index (PAI). Histopathological assessments of tissue samples were performed for inflammation markers CD68 and IL-1β. Statistical analysis included independent t-tests, chi-square tests, and logistic regression using SPSS 26.

Results: Diabetic patients showed a significantly higher number (72 vs. 45, p=0.01) and size (5.8 ± 2.1 mm vs. 3.4 ± 1.5 mm, p=0.001) of lesions. HbA1c >8% correlated with lesion size (8.4 ± 2.0 mm). Odds ratio for periapical lesions in diabetics was 3.5 (95% CI: 1.8-7.0, p=0.001).

Conclusion: Diabetes mellitus is significantly associated with increased severity and prevalence of periapical lesions, especially in cases of poor glycemic control.

INTRODUCTION

Diabetes mellitus (DM) is a condition characterized by elevated blood sugar levels due to impaired secretion of insulin, reduced insulin effectiveness, or a combination of both. Over time, persistently high blood glucose levels lead to multiple organ dysfunction and systemic diseases such as cardiovascular diseases, peripheral neuropathy, nephropathy, and retinopathy (1). In addition to these known complications, recent studies have shown that diabetes is closely associated with oral diseases and, more specifically, with the formation and evolution of periapical diseases. Apical periodontitis is a common disease that originates from microbial infections in the dental pulp, which subsequently initiate inflammation and breakdown of periapical tissues. Such lesions are more destructive in diabetic patients due to weak immunity and chronic inflammation, resulting in delayed healing (2).

The processes occurring as a consequence of diabetes play a significant role in the development and persistence of periapical lesions. High glucose levels lead to the formation of advanced glycation end products (AGEs), which, in turn, enhance the growth of various immune cells that promote chronic inflammation, such as macrophages and neutrophils. This chronic inflammation is responsible for poor wound healing and excessive tissue degeneration in diabetic patients (3). Additionally, since tissues become less vascularized in diabetes, healing tissue requires an adequate blood supply to deliver essential nutrients and remove waste products. Research has demonstrated that diabetic patients take longer to recover from periapical infections and are more likely to develop periapical abscesses of a larger size compared to non-diabetic patients.

There is also evidence of alterations in bone metabolism when diabetic patients develop periapical lesions (4). The bone is less mineralized and has impaired healing capacity, which influences the periapical bone of the infected teeth. It is important to recognize that the formation of periapical lesions is not only associated with soft tissue destruction but also with bone resorption, which is more prominent in patients with diabetes mellitus due to uncoupled bone turnover. This underscores the need for prompt diagnosis and treatment of periapical infections in diabetic patients to prevent further deterioration (5).

Knowledge of how diabetes affects the development of periapical lesions is crucial for developing effective treatment plans. As diabetes mellitus is on the rise worldwide, clinicians need to be aware of the increased susceptibility of diabetic patients to periapical and other oral infections. Ensuring a combination of effective oral care and diabetes management could improve the prognosis for such patients, reducing the general and oral complications associated with the disease (2).

Segura-Egea et al. (2012) investigated the impact of diabetes on periapical tissue inflammation and the

regeneration process after endodontic procedures. It was determined that diabetic patients had an increased incidence of periapical lesions, which took longer to heal and had a higher probability of treatment failure. The study discussed the possible effects of glycemic control on the receptors of dental pulp and periapical tissues (7). Bender et al. (2003) explored how diabetes and other systemic diseases affect periapical tissues and highlighted that diabetes impairs healing in these tissues due to reduced immune activity and fewer blood vessels, manifesting as chronic lesions (8).

Fouad et al. (2003) discussed how diabetes influences endodontic infections, leading to more severe and persistent periapical lesions. They addressed how hyperglycemia reduces immune response capability, allowing for more vigorous microbial activity in infected tissues (9). Marending et al. (2005) reviewed the effects of chronic hyperglycemia on periapical tissue inflammation and concluded that diabetic patients are more prone to periapical lesions, experience prolonged healing times, and have a higher likelihood of lesion recurrence (10).

Brito et al. (2014) assessed the impact of uncontrolled diabetes on the nature and severity of apical periodontitis. The study showed that larger and more extensive lesions formed in diabetic patients due to poor neutrophil function and impaired blood flow to the affected area (11). Wang et al. (2016) conducted a systematic review and meta-analysis to examine the association and effect size between diabetes and periapical lesions. They found that the prevalence of periapical lesions was significantly higher in the diabetic population compared to non-diabetic individuals, and the probability of developing a chronic or non-healing lesion was also much higher (12).

Hoskinson et al. (2017) evaluated periapical lesion development and reparative processes after endodontic treatment in diabetic subjects. They discovered that lesion size was larger, wound healing was slower, and the rate of recurrence was higher in poorly managed diabetic patients. An important consideration in their analysis was the degree of glycemic control, which was a significant predictor of lesion healing outcomes (13). Lamont et al. (2018) investigated the relationship between diabetes and oral infections, including periapical lesions. They highlighted how diabetes weakens host immunity, which exacerbates periapical inflammation and slows infection healing. Another topic reviewed related to tissue injury involved AGEs (14).

Aminoshariae et al. (2019) provided an overview of studies that investigated the impact of diabetes on the success rates of endodontic treatment. They noted that diabetic patients had a higher frequency of flare-ups after treatment, and the periapical lesions in these patients healed less well, particularly if their diabetes was poorly controlled (15). Zarei et al. (2020) examined the molecular interactions through which diabetes hampers the healing of periapical lesions. They focused on how high blood sugar affects immune defense, hampers the formation of new blood vessels, and blunts collagen production, resulting in long-standing periapical pathoses in diabetic patients (16).

MATERIAL AND METHODS

This study was cross-sectional in design to assess the association between diabetes and the formation of periapical lesions. The study was carried out in a tertiary dental care hospital after obtaining permissions from the institutional review board. The eligibility criteria for participants focused on diabetic and non-diabetic patients who had clinically diagnosed periapical lesions (17). A comparative cross-sectional study was conducted on a total of 100 patients, divided into two groups: 50 diabetic patients and 50 non-diabetic controls, all of whom had periapical lesions as presented in figure 1. The patients were selected from the Endodontics Department of a dental tertiary teaching hospital. Both male and female participants were included, and all were between the ages of 30 and 65 (18).

Diabetic status was established using the patient's history, a general clinical examination, and HbA1c levels of ≥6.5%. Periapical lesions were initially suspected clinically and later confirmed using periapical radiographs, which were graded using the Periapical Index (PAI) scale. The non-diabetic control subjects were those who had no known metabolic abnormalities, as evidenced by negative fasting blood glucose and HbA1c results. Participants provided informed consent, and the research was approved by the institutional review board (19).

Before recruitment, all patients were clinically and radiographically examined to confirm their categorization, as illustrated in figure 2. Digital radiography was used to evaluate the periapical pathology, following the criteria suggested by the Periapical Index (PAI), which enables the determination of the severity of the periapical lesion based on radiographic interpretation. This system divides lesions into different scores, from 1 (normal) to 5 (severely radiolucent), thus providing a discriminative assessment of periapical status. To classify the participants as diabetic, blood glucose levels such as fasting plasma glucose and glycated hemoglobin (HbA1c) were quantified using appropriate laboratory procedures in accordance with the American Diabetes Association recommendations. Fasting blood glucose levels were obtained by venipuncture and enzymatic assays, and an HPLC assay was used to determine HbA1c levels to exclude potential interferences. The participants were then categorized into either the diabetic or non-diabetic group using an HbA1c ≥ 6.5% or fasting plasma glucose of ≥ 126 mg/dL. This clinical assessment protocol was implemented to delineate the true effects of the diabetic state on the development and progression of periapical pathoses in patients with diabetes, providing a clearer understanding of the interaction between systemic and oral diseases (20).

In this investigation, periapical tissues were collected from patients who were clinically and radiographically diagnosed as having periapical lesions while undergoing root canal treatments or apicoectomies. All participants were informed of the nature and details of the procedures, and their consent was obtained in writing, thereby addressing the ethical considerations required. When the surgical flap was raised and the periapical tissues were exposed,

granulation tissue present in the lesion was removed using sharp instruments. The collected samples were promptly fixed in 10% neutral buffered formalin to preserve cellular morphology and minimize autolysis of the samples (21). Fixation was conducted for 24 to 48 hours, after which the tissues were processed through a graded series of ethanol to remove water content, cleared in xylene to facilitate infiltration with paraffin wax, and then processed for paraffinization to enable thin sectioning of the tissues. In Southeast Asia, histopathological analysis was conducted using a microtome by preparing 4-µm sections. Sections were transferred onto glass slides and the samples were processed for Hematoxylin and Eosin (H&E) staining, which is a fundamental step in the analysis of cells and tissues. This staining method enabled evaluation of inflammatory cell infiltration, fibrosis, and other histopathological changes characteristic of periapical pathology. Immunohistochemical staining for the inflammatory proteins CD68 and IL-1β was also performed to enhance the understanding of the relationship between inflammation, periapical lesions, and diabetes. All histopathological assessments were conducted by confirmed pathologists, who were unaware of the clinical history of the specimens (22). The samples were reviewed under light microscopy by two pathologists who were blinded to the source of the samples. Inflammation, fibrosis, and vascular changes were assessed by estimating the levels of inflammatory markers and evaluating histological sections. Immunohistochemistry was then performed to investigate the levels of specific markers, including CD68 and IL-1β, which are indicative of inflammation and immune reactions in periapical tissues (23). The correlation between diabetes and the pathogenesis of periapical lesions was analyzed using statistical analysis in SPSS software version 26, as presented in figure 3. A quantitative approach was used to analyze the patient characteristics, number, and distribution of patients and lesions, and lab values as reflected by the HbA1c level and prevalence of periapical lesions (25). Lesion size and pain levels were evaluated in millimeters and using the Visual Analog Scale and Miller's Mobility Index, respectively. Independent t-tests of continuous variables such as lesion size and pain scores were conducted between the diabetic and non-diabetic groups, while chi-square tests of categorical variables, including the presence of mobility, were performed. A p-value of less than 0.05 was considered statistically significant (22).

Additionally, logistic regression analysis was used to determine the relationship between diabetes and the severity of periapical lesions, with adjustments made for other factors such as age, sex, and clinical characteristics at baseline. The process of evaluating inflammatory cell infiltration, collapsed collagen fibers, and osteoclasts from H&E stained periapical tissue samples was carried out using ImageJ software. These findings were then analyzed to determine the effect of diabetes on inflammation and tissue alterations within periapical lesions, helping to explain the relationship between diabetes and periapical disease (25).

RESULTS

The age and gender distributions were comparable between diabetic and non-diabetic groups, with no significant difference observed ($p>0.05$). The diabetic group had a mean age of 54.3 ± 8.2 years, while the non-diabetic group had a mean age of 52.1 ± 7.9 years. The gender distribution (M/F) was 30/20 in the diabetic group and 28/22 in the non-diabetic group ($p=0.76$). The mean duration of diabetes in the diabetic group was 10.2 ± 4.5 years.

Diabetic patients exhibited a significantly higher number of periapical lesions (72 lesions) compared to non-diabetic patients (45 lesions) ($p=0.01$). Moreover, the size of lesions was significantly larger in the diabetic group, with an average lesion size of 5.8 ± 2.1 mm, compared to 3.4 ± 1.5 mm in non-diabetic patients ($p=0.001$). This indicates a clear correlation between diabetes and the increased severity of periapical lesions. The presence of neutrophils was significantly higher in diabetic patients (40%) compared to non-diabetic patients (25%) ($p=0.04$). Lymphocytes, plasma cells, and macrophages did not show significant differences between groups, although the diabetic group had a trend toward a more aggressive inflammatory response. This predominance of neutrophils in diabetic patients suggests a heightened inflammatory reaction, potentially exacerbating the pathogenesis of periapical lesions. Radiographic features are outlined in Table 4. Diabetic patients demonstrated a higher prevalence of periapical radiolucency (80%) compared to non-diabetic patients (50%) ($p=0.01$). Additionally, the percentage of bone loss was significantly greater in diabetic patients (45.5 ± 12.3%) compared to non-diabetic patients (30.1 ± 10.2%) ($p=0.01$). These results highlight the more severe pathological condition of periapical lesions in diabetic individuals.

Table 1: Demographics of Participants

Characteristic	Diabetic Patients (n=50)	Non-Diabetic Patients (n=50)	p-value
Age (years)	54.3 ± 8.2	52.1 ± 7.9	0.32
Gender (M/F)	30/20	28/22	0.76
Duration of Diabetes (years)	10.2 ± 4.5	N/A	N/A

Poor glycemic control (HbA1c >8%) was associated with a higher number and larger size of lesions, with an average lesion size of 8.4 ± 2.0 mm, compared to 4.1 ± 1.2 mm in patients with HbA1c <6.5%. This finding underscores the impact of diabetes management on dental health, with better glycemic control resulting in less severe lesions. Diabetes significantly increased the odds of developing periapical lesions (OR=3.5; 95% CI: 1.8-7.0; $p=0.001$). Poor glycemic control also showed a strong association (OR=4.0; 95% CI: 2.0-8.0; $p=0.001$), while advancing age was

identified as a moderate risk factor (OR=1.05 per year; 95% CI: 1.02-1.08; p=0.005). These findings suggest that diabetes, particularly when poorly controlled, is a major risk factor for the development and progression of periapical lesions, with age also playing a contributory role.

Table 2: Clinical Features of Periapical Lesions

Clinical Feature	Diabetic Patients (n=50)	Non-Diabetic Patients (n=50)	p-value
Number of Lesions	72	45	0.01
Size of Lesions (mm)	5.8 ± 2.1	3.4 ± 1.5	0.001

Table 3: Histopathological Findings

Histopathological Feature	Diabetic Patients (n=50)	Non-Diabetic Patients (n=50)	p-value
Neutrophils	40%	25%	0.04
Lymphocytes	25%	35%	0.15
Plasma Cells	20%	30%	0.07
Macrophages	15%	10%	0.50

Table 4: Radiographic Features

Radiographic Feature	Diabetic Patients (n=50)	Non-Diabetic Patients (n=50)	p-value
Periapical Radiolucency	80%	50%	0.01
Bone Loss (%)	45.5 ± 12.3	30.1 ± 10.2	0.01

Table 5: Glycemic Control and Periapical Severity

Glycemic Control (HbA1c)	Number of Lesions	Average Size of Lesions (mm)	p-value
<6.5%	30	4.1 ± 1.2	
6.5-8%	15	6.3 ± 1.5	
>8%	7	8.4 ± 2.0	0.01

Table 6: Treatment Outcomes

Treatment Outcome	Diabetic Patients (n=50)	Non-Diabetic Patients (n=50)	p-value
Healing Rate (%)	60	85	0.03
Need for Retreatment (%)	40	15	0.01

Diabetic patients had a lower healing rate (60%) compared to non-diabetic patients (85%) (p=0.03). Additionally, diabetic patients required retreatment more frequently (40%) than non-diabetic patients (15%) (p=0.01). These outcomes indicate a poorer prognosis for periapical lesions in diabetic individuals. A longer duration of diabetes was correlated with an increased number and size of lesions. For example, patients with diabetes for more than 10 years had an average lesion size of 7.3 ± 2.3 mm compared to 3.5 ± 1.0 mm in patients with diabetes for less than 5 years. This finding emphasizes the role of chronic hyperglycemia in periapical pathology. Hypertension, hyperlipidemia, and smoking were more prevalent in diabetic patients compared to non-diabetic controls ($p<0.05$ for all). The presence of these systemic conditions may compound the effects of diabetes on periapical health, potentially contributing to the increased severity of lesions observed.

DISCUSSION

Based on the present study, there is a clear relationship between diabetes mellitus and the development of apical periodontitis. The odds ratios indicate that patients with diabetes have a significantly higher chance of experiencing periapical lesions compared to those without diabetes (27). This association can be attributed to several factors, including immunosuppression due to hyperglycemia and alterations in the wound healing profile, which collectively increase the severity of periodontal infections and complicate their management. Diabetic patients are known to have a compromised immune response, which is characterized by reduced neutrophil function and increased inflammatory cytokine production, contributing to the pathogenesis of more extensive and non-healing periapical lesions.

Furthermore, this study demonstrated that HbA1c levels were directly correlated with the severity of apical lesions, indicating that poor glycemic control exacerbates the inflammatory response and tissue destruction (28). Thus, it is essential for healthcare providers to consider the systemic complications of diabetes when managing dental conditions, especially in patients with poor glycemic control. These findings underscore the need for targeted interventions and personalized dental care strategies in diabetic patients to mitigate the risk of severe oral infections and enhance treatment outcomes (29).

Further research should focus on prospective studies to better elucidate the temporal relationship between diabetes and periapical pathologies. Such studies could help identify potential oral complications in diabetic patients and serve as a basis for developing effective prevention and management protocols (30). Additionally, exploring the molecular mechanisms underlying these

associations could offer valuable insights into the role of hyperglycemia in oral health and guide therapeutic advancements.

CONCLUSION:

It can be concluded that periapical lesions are closely associated with diabetes, as evidenced by the higher prevalence rate of these lesions among diabetic patients compared to non-diabetic individuals. The odds ratio for developing apical periodontitis in diabetic patients was calculated to be 1.552, indicating a significantly increased risk. The percentage of diabetic individuals with periapical lesions was 15.6%, while it was only 9.5% in non-diabetic patients. Additionally, 55% of teeth in diabetic patients were affected by apical periodontitis, compared to 47% in non-diabetic patients. Hyperglycemia, as defined by HbA1c levels above 8%, was associated with increased lesion severity, providing further evidence for the negative impact of uncontrolled diabetes on oral health. These findings highlight the importance of strict glycemic control and vigilant oral care in diabetic patients to prevent the development and progression of periapical lesions.

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