Glycated Hemoglobin Levels and Prevalence of Apical Periodontitis in Type 2 Diabetic Patients

Benito Sánchez-Domínguez, DDS,* José López-López, MD, DDS, Phd,† Enric Jané-Salas, MD, DDS, Phd,‡ Lizett Castellanos-Cosano, DDS, Phd,* Eugenio Velasco-Ortega, MD, DDS, Phd,§ and Juan José Segura-Egea, MD, Phd, DDS*

Abstract

Introduction: The purpose of this investigation was to study the possible association between the prevalence of apical periodontitis (AP) and the glycemic control of type 2 diabetic patients. Methods: In a cross-sectional study, the radiographic records of 83 type 2 diabetic patients were examined. Glycemic control was assessed by the mean glycated hemoglobin (HbA1c level). AP was diagnosed as radiolucent periapical lesions (RPLs) using the periapical index score. The Student t test, chi-square test, and logistic regression analysis were used in the statistical analysis. Results: Based on the HbA1c levels, 2 groups of diabetic patients were established: the HbA1c good control group (GCG, n = 24, HbA1c <<6.5%) and the HbA1c poor control group (PCG, n = 59, HbA1c ≥6.5%). In the total sample, RPLs in 1 or more teeth were found in 62.7%, and no significant differences between GCG and PCG groups were observed (P = .13). At least 1 root-filled tooth was found in 32.5% of diabetic patients; this percentage was comparable in both HbA1c groups (P = .68). The prevalence of RPLs in RFT (29.6%) was similar in the GCG compared with the PCG (P = .94). Multivariate logistic regression analysis showed that worse periapical status correlated significantly with HbA1c levels ≥6.5% in type 2 diabetic patients (odds ratio = 3.8; 95% confidence interval, 1.1–13.0; P = .03). Conclusions: HbA1c levels of diabetic patients are associated with periapical status. Data reported in the present study, together with the results of previous studies, further support a relationship between glycemic control and periapical inflammation in diabetic patients. (J Endod 2015;□:1–6)

Key Words

Apical periodontitis, diabetes mellitus, endodontics, glycemic control, glycosylated hemoglobin, periapical inflammatory response

From the *Department of Stomatology, School of Dentistry, University of Sevilla, Sevilla; and †Department of Odonto-stomatology, School of Dentistry, University of Barcelona, Barcelona, Spain. Address requests for reprints to Dr Juan J. Segura-Egea, Facultad de Odontología, Universidad de Sevilla, 41009-Sevilla, Spain. E-mail address: segurajj@us.es 0099-2399/$ - see front matter Copyright © 2015 American Association of Endodontists. http://dx.doi.org/10.1016/j.joen.2014.12.024

Apical periodontitis (AP) is an acute or chronic inflammatory lesion around the apex of a tooth caused by bacterial infection of the pulp canal system (1). Periapical inflammatory response provokes a characteristic local periradicular osteolytic radiolucent lesion, but AP is not exclusively a locally limited phenomenon. Lipopolysaccharide from anaerobic gram-negative bacteria causing AP activates the innate immune system (2), up-regulating proinflammatory cytokines such as interleukin (IL)-1β, IL-6, IL-8, tumor necrosis factor α, and prostaglandin E2 (PGE2). These cytokines may be released into systemic circulation (3), inducing or perpetuating an elevated chronic systemic inflammatory status (4, 5).

Diabetes mellitus (DM) is a clinically and genetically heterogeneous group of disorders affecting the metabolism of carbohydrates, lipids, and proteins in which hyperglycemia is a main feature (6). Glycated hemoglobin (HbA1c) has been used as a “gold standard” for mean glycemia and as a measure of risk for the development of DM complications (4, 6). The American Association of Clinical Endocrinologists considers HbA1c levels ≤6.5% as a goal for optimal glycemic control in diabetic patients (7).

DM is caused by a deficiency in insulin secretion caused by pancreatic β-cell dysfunction and/or insulin resistance in liver and muscle (8). It has been shown that proinflammatory status resulting from the activation of innate immunity pathways contributes to insulin resistance (9, 10). Therefore, it has been suggested that the ongoing cytokine-induced acute-phase response, a low-grade inflammation that occurs through activation of the innate immune system in chronic oral inflammatory processes such as periodontal (4) and endodontic diseases (11), could contribute to increased insulin resistance and poor glycemic control in diabetic patients.

Some studies have investigated the association between periodontal disease and diabetes-related inflammatory status (4, 12, 13). Moreover, the relationship of HbA1c levels with periodontal disease has been extensively analyzed, and several studies have been conducted to assess the possible effect of nonsurgical periodontal treatment on serum glycated hemoglobin in diabetic patients (13, 14). In the case of AP, several investigations have studied, both in animals (15, 16) and humans (17–24), the possible association between AP and DM, with inconclusive results (11). However, as far as we know, no study has investigated whether AP is connected to the metabolic control of diabetic patients, analyzing the correlation of HbA1c levels with the periapical status of diabetic patients.

The purpose of this investigation was to study the possible association between the prevalence of AP, diagnosed as radiolucent periapical lesions (RPLs), and the glycemic control of type 2 diabetic patients assessed by the mean HbA1c level. We tested the null hypothesis that “AP is not associated with glycemic control in diabetic patients.”

Materials and Methods

Participants were recruited among patients presenting consecutively seeking routine dental care (not emergency care) at the University of Barcelona dental clinic between the years 2011 and 2013. Subjects reporting a history of type 2 DM, diagnosed according to the criteria of the American Diabetes Association (2010) (6), were asked to voluntarily participate. Inclusion criteria were as follows: patients older than 18 years.
having at least 8 remaining teeth with HbA1c levels recorded in the last week who agreed to a radiologic examination. Exclusion criteria were patients younger than 18 years old, patients having less than 8 remaining teeth, patients without HbA1c levels recorded in the last week, and patients who did not agree to a radiologic examination. A total of 83 subjects (66.0 ± 10.6 years), 41 men (49.4%) and 42 women (50.6%), who agreed and met the inclusion/exclusion criteria were included in the study. Questionnaires were filled out for each patient, eliciting information on medical and dental history, the most recent measurement of HbA1c levels, smoking status, periodontal status, and coronary heart disease.

The criteria used to determine the presence of periodontal disease were those previously established by Machtei et al (25); patients showing more than 5% gingival bleeding with clinical attachment loss higher than 6 mm in 2 or more sites and with 1 or more sites with a probing depth ≥ 5 mm were diagnosed as having periodontal disease.

The ethics committee of the faculty of dentistry approved the study, and all the patients provided written informed consent. The research was conducted in full accordance with the World Medical Association Declaration of Helsinki.

**Clinical Research**

**Glycemic Control Assessment**

To determine the metabolic control status of diabetic patients, HbA1c was registered. Adequate glycemic control was defined according to the American Association of Clinical Endocrinologists as HbA1c <6.5% (7) using the most recent HbA1c measurement before the visit date obtained from the patient’s record on the public health service. Based on the HbA1c levels, 2 groups were established: the HbA1c good control group (GGG) (HbA1c <6.5%) and the HbA1c poor control group (PGG) (HbA1c ≥6.5%).

**Radiographic Examination and Evaluation**

Radiographic periapical status was diagnosed on the basis of examination of digital panoramic radiographs of the jaws. Two trained radiographic technicians, with over 10 years of experience, took the panoramic radiographs using a digital orthopantomograph machine (Promax, Planmeca, class I, type B, 80 kHz, Planmeca, Helsinki, Finland).

All teeth, excluding third molars, were recorded. Teeth were categorized as root-filled teeth (RFTs) if they had been filled with a radiopaque material in the root canal(s). For each subject, the number of teeth present, the number and location of RFTs, and the number and location of teeth having identifiable RPLs were recorded.

The periapical status was assessed using the periapical index (PAI) score (26) as described previously (27). A score greater than 2 (PAI ≥ 5) was considered to be a sign of AP. The worst score of all roots was taken to represent the PAI score for multirooted teeth.

**Observer Calibration**

Three observers with extensive clinical experience in endodontics examined the radiographs. Before evaluation, the observers participated in a calibration course for the PAI system, which consisted of 100 radiographic images of teeth, some root filled and some not, kindly provided by Dr. Ørstavik. Each tooth was assigned to 1 of the PAI scores by using visual references (also provided by Dr. Ørstavik) for the 5 categories within the scale. After scoring the teeth, the results were compared with a “gold standard atlas,” and a Cohen kappa was calculated (0.79–0.87).

Intraobserver reproducibility was evaluated for each examiner. Every observer scored the panoramic radiographs of 20 patients (10 in each group, randomly selected). Then, 1 month after this first examination, the observer was recalibrated in the PAI system and repeated the scoring of the radiographs of the same 20 patients. The intraobserver agreement test on PAI scores on the 20 patients produced a Cohen kappa ranging from 0.82 to 0.93.

Finally, intraobserver reproducibility was also determined by comparing the PAI scores on the 20 radiographs provided by each observer. The agreement test produced a Cohen kappa ranging from 0.84 to 0.91. The Cohen kappa for interobserver variability ranged from 0.80 to 0.89. The consensus radiographic standard was the simultaneous interpretation by the 3 examiners of the panoramic radiograph of each patient.

**Statistical Analysis**

The minimal sample size (adjusted n = 72) was calculated for the comparison of proportions with nQuery Advisor (version 7.0; Statistical Solutions Ltd, Cork, Ireland), taking into account a 2-sided significance level of 5% (α = 0.05, 2αα = 1.960) and an 80% statistical power (β = 0.20, Zβ = 0.842) to detect a hypothesized difference between groups of 25 points and a 15% dropout rate.

Raw data were entered into Excel (Microsoft Corp, Redmond, WA). All analyses were performed in an SPSS environment (version 11; SPSS Inc, Chicago, IL). Data are reported as mean ± standard deviation. The Student t test and chi-square test were used to determine the significance of differences between groups. Logistic regression analysis was performed to measure the strength of the association between HbA1c levels and the presence of RPLs, adjusting for the presence of covariates. A value of P < .05 was considered significant.

**Results**

The characteristics and dental status of diabetic type 2 patients in relation with their HbA1c levels are shown in Table 1. In the total sample, 49% were men and 51% were women, and the mean age was 66.6 ± 10.6 years. The average number of teeth per subject was 21.1 ± 6.1, and the mean number of RFTs and teeth with RPLs per subject was 0.7 ± 1.3 and 1.7 ± 2.2, respectively. Twenty patients (24.1%) were smokers, 67 (80.7%) had coronary heart disease, and 72 (86.7%) had periodontal disease. According to HbA1c levels, patients were classified into 2 groups: 24 (28.9%) were included in the HbA1c GGG (HbA1c <6.5%), and 59 (71.1%) were classified in the HbA1c PGG (HbA1c ≥6.5%). No statistically significant differences between the 2 groups were observed in age, sex, smoking habits, coronary heart disease, periodontal status, number of teeth, number of RFTs, or number of teeth with RPLs (P > .05).

The relationship between glycemic control of diabetic patients, assessed as HbA1c levels, and radiographic periapical status was analyzed (Table 2). RPLs in 1 or more teeth were found in 52 diabetic patients (62.7%); 40 patients (67.8%) showed at least 1 RPL in the PGG, whereas this percentage was only 50.0% in the GGG (odds ratio = 2.1; 95% confidence interval [CI], 0.8–5.5; P = .13). The frequency of root canal treatment was 32.5% (27 diabetic patients) in the total sample, and no statistically significant differences between the PGG and GGG were observed (odds ratio = 1.2; 95% CI, 0.4–3.5; P = .68). Finally, among diabetic patients with RFTs, 8 (29.6%) had at least 1 RFT showing RPL, but the prevalence of RPLs was not significantly higher in the PGG compared with the GGG (odds ratio = 1.2; 95% CI, 0.2–7.5; P = .94).

Multivariate logistic regressions were run with age, sex, smoking habits, number of teeth, periodontal status, periapical status, and endodontic status as independent explanatory variables and HbA1c levels as the dependent variable (0 = HbA1c <6.5%; 1 = HbA1c ≥6.5%)
In this cross-sectional study, the possible association between the prevalence of radiographic AP and HbA1c levels in diabetic patients has been analyzed. The null hypothesis tested (ie, that AP is not associated with glycemic control in diabetic patients) has been refused. The results of the final logistic regression model reveal a significantly higher prevalence of AP in type 2 diabetic patients, with HbA1c levels $>6.5\%$ ($P = .03$). This is the first report showing an association between periapical status and glycemic control in diabetic patients.

The recruitment method of the patients was similar to that used in previous studies (19–21) (ie, subjects presenting consecutively seeking routine dental care [not emergency care] at the dental service of the faculty of dentistry). Diabetes was diagnosed according to the current criteria for the diagnosis of diabetes (6, 7). The estimation of blood level of HbA1c provides an accurate and objective measure of blood glucose levels in the previous 30 to 90 days. Glycated hemoglobin levels are increased in diabetic patients by the slow nonenzymatic covalent attachment of glucose and other sugars (glycation), with the rate of formation of HbA1c directly proportional to blood glucose concentrations. Nondiabetic subjects have HbA1c levels of less than 6%, whereas levels in poorly controlled patients are $\geq 6.5\%$ and can be as great as 20% (28). In the present study, only 24 diabetic patients (28.9%) had HbA1c levels $\geq 6.5\%$ and were included in the GCG. The other type 2 diabetics (29.6%) had well-controlled HbA1c levels ($< 6.5\%$) and were included in the PCG. The results did not show statistically significant differences between the 2 groups in age, sex, smoking habits, coronary heart disease, number of teeth, number of RFT, or number of teeth with RPLs ($P > .05$).

The prevalence of periodontal disease in the total sample was high (86.7%). This result agrees with the well-established association between periodontal disease and diabetes mellitus (29). Moreover, it has been shown that the presence of periodontal disease correlated with worse glycemic control over time, increasing HbA1c levels (4). Taking into account that in the present study both groups, the GCG and the PCG, showed similar frequency of periodontal disease ($P < .05$), periodontal disease is not acting as a confounding factor.

To assess the presence of AP, panoramic radiographs and the PAI (26) were used. It has been reported that an underestimation of lesions occurred when panoramic radiography was used (30), but the difference with periapical radiography was not statistically significant (31). Although both periapical and panoramic radiography have been used to assess the periapical status in experimental and epidemiologic

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**TABLE 1.** Characteristics and Dental Status of Diabetic Patients in Relation with Their HbA1c Levels

<table>
<thead>
<tr>
<th></th>
<th>GCG HbA1c $&lt;6.5%$ ($n = 24, 28.9%$)</th>
<th>PCG HbA1c $\geq 6.5%$ ($n = 59, 71.1%$)</th>
<th>Total ($N = 83, 100%$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>67.2 $\pm$ 10.8</td>
<td>65.5 $\pm$ 10.6</td>
<td>66.6 $\pm$ 10.6$^*$</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>12 (50.0)</td>
<td>29 (49.0)</td>
<td>41 (49.0)$^*$</td>
</tr>
<tr>
<td>Female</td>
<td>12 (50.0)</td>
<td>30 (51.0)</td>
<td>42 (51.0)$^*$</td>
</tr>
<tr>
<td>Smoking habits, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3 (12.5)</td>
<td>17 (28.8)</td>
<td>20 (24.1)$^*$</td>
</tr>
<tr>
<td>No</td>
<td>21 (87.5)</td>
<td>42 (71.2)</td>
<td>63 (75.9)</td>
</tr>
<tr>
<td>Coronary heart disease, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>18 (75.0)</td>
<td>49 (83.1)</td>
<td>67 (80.7)$^*$</td>
</tr>
<tr>
<td>No</td>
<td>6 (25.0)</td>
<td>10 (16.9)</td>
<td>16 (19.3)</td>
</tr>
<tr>
<td>Number of teeth</td>
<td>19.9 $\pm$ 6.3</td>
<td>21.5 $\pm$ 6.0</td>
<td>21.1 $\pm$ 6.1$^*$</td>
</tr>
<tr>
<td>Number of RFTs</td>
<td>0.5 $\pm$ 1.3</td>
<td>0.7 $\pm$ 1.3</td>
<td>0.7 $\pm$ 1.3$^*$</td>
</tr>
<tr>
<td>Number of teeth with RPLs</td>
<td>1.5 $\pm$ 2.2</td>
<td>1.7 $\pm$ 2.2</td>
<td>1.7 $\pm$ 2.2$^*$</td>
</tr>
<tr>
<td>Periodontal disease, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>23 (95.8)</td>
<td>49 (83.1)</td>
<td>72 (86.7)$^*$</td>
</tr>
<tr>
<td>No</td>
<td>1 (4.2)</td>
<td>10 (16.9)</td>
<td>11 (13.3)</td>
</tr>
<tr>
<td>HbA1c levels</td>
<td>6.0 $\pm$ 0.5</td>
<td>7.8 $\pm$ 1.3</td>
<td>7.3 $\pm$ 1.4$^+$</td>
</tr>
</tbody>
</table>

CI, confidence interval; GCG, good control group; HbA1c, glycated hemoglobin; PCG, poor control group.

$^*$Chi-square test, $P > .05$.

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**TABLE 2.** Distribution of Radiolucent Periapical Lesions (RPLs), Root-filled Teeth (RFTs), and RFTs with RPLs (RFT-RPL) in Both Groups of Diabetic Patients

<table>
<thead>
<tr>
<th></th>
<th>GCG (HbA1c $&lt;6.5%$)</th>
<th>PCG (HbA1c $\geq 6.5%$)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least 1 RPL, n (%)</td>
<td>12 (50.0)</td>
<td>40 (67.8)</td>
<td>52 (62.7)</td>
</tr>
<tr>
<td>No RPLs, n (%)</td>
<td>12 (50.0)</td>
<td>39 (61.2)</td>
<td>51 (61.3)</td>
</tr>
<tr>
<td>Total</td>
<td>24</td>
<td>79</td>
<td>103</td>
</tr>
<tr>
<td>Odds ratio</td>
<td>1.0</td>
<td>2.1$^*$</td>
<td>2.2$^*$</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.8–5.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least 1 RFT, n (%)</td>
<td>7 (29.2)</td>
<td>20 (33.9)</td>
<td>27 (32.5)</td>
</tr>
<tr>
<td>No RFTs, n (%)</td>
<td>17 (70.8)</td>
<td>39 (66.1)</td>
<td>56 (67.5)</td>
</tr>
<tr>
<td>Total</td>
<td>24</td>
<td>58</td>
<td>82</td>
</tr>
<tr>
<td>Odds ratio</td>
<td>1.0</td>
<td>1.2$^*$</td>
<td>1.2$^*$</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.4–3.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least 1 RFT-RPL, n (%)</td>
<td>2 (8.6)</td>
<td>6 (10.6)</td>
<td>8 (9.6)</td>
</tr>
<tr>
<td>No RPLs, n (%)</td>
<td>5 (21.4)</td>
<td>14 (23.7)</td>
<td>19 (23.0)</td>
</tr>
<tr>
<td>Total</td>
<td>7</td>
<td>20</td>
<td>27</td>
</tr>
<tr>
<td>Odds ratio</td>
<td>1.0</td>
<td>1.1$^*$</td>
<td>1.1$^*$</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.2–7.5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cl, confidence interval; GCG, good control group; HbA1c, glycated hemoglobin; PCG, poor control group.
Clinical Research

TABLE 3. Multivariate Logistic Regression Analysis of the Association of the Independent Variables Age, Sex, Smoking, Number of Teeth, Periodontal Status, Periapical Status, and Endodontic Status on the Dependent Variable HbA1c Levels

<table>
<thead>
<tr>
<th>Explanatory variable</th>
<th>B</th>
<th>P value</th>
<th>Odds ratio</th>
<th>CI 95% inf limit</th>
<th>CI 95% sup limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>−0.0137</td>
<td>.6219</td>
<td>0.9864</td>
<td>0.9339</td>
<td>1.0417</td>
</tr>
<tr>
<td>Sex</td>
<td>−0.4676</td>
<td>.3995</td>
<td>0.6265</td>
<td>0.2111</td>
<td>1.8593</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.1626</td>
<td>.1254</td>
<td>3.1982</td>
<td>0.7231</td>
<td>14.1448</td>
</tr>
<tr>
<td>Teeth number</td>
<td>0.0250</td>
<td>.5840</td>
<td>1.0253</td>
<td>0.9375</td>
<td>1.1214</td>
</tr>
<tr>
<td>Periodontal status</td>
<td>−1.7329</td>
<td>.1366</td>
<td>0.1768</td>
<td>0.0180</td>
<td>1.7312</td>
</tr>
<tr>
<td>Periapical status</td>
<td>1.2841</td>
<td>.0492</td>
<td>3.6116</td>
<td>1.0043</td>
<td>12.9882</td>
</tr>
<tr>
<td>Endodontic status</td>
<td>1.1683</td>
<td>.0952</td>
<td>3.2813</td>
<td>0.8127</td>
<td>13.2495</td>
</tr>
</tbody>
</table>

B, B coefficient in logistic regression; CI, confidence interval; HbA1c, glycated hemoglobin; inf, inferior; sup, superior.
Overall model fit: $\chi^2 = 11.6, P = .12$. For sex, 0 = women and 1 = men; for smoking, 0 = nonsmoker and 1 = smoker; for periodontal status, 0 = absent periodontal disease and 1 = present periodontal disease; for periapical status, 0 = no tooth with radiolucent periapical lesion and 1 = 1 or more tooth with radiolucent periapical lesion; for endodontic status, 0 = no root-filled teeth and 1 = 1 or more root-filled teeth; and for HbA1c levels, 0 = HbA1c <6.5% and 1 = HbA1c ≥6.5%.

studies, the fact that all teeth can be seen on 1 panoramic radiograph, the relatively low exposure to ionizing radiation (considering that the radiation dose from a panoramic radiograph approximately corresponds to 2–4 intraoral radiographs (31), the convenience of panoramic radiographs and the speed with which they can be obtained are advantageous when compared with full-mouth periapical radiographs (32). Thus, panoramic radiography is a highly viable tool to implement studies in a rapid fashion (33), and many epidemiologic studies have been performed using panoramic radiographs (22–24, 27, 34, 35). On the other hand, although the PAI score system was first described for periapical radiographs (26), it has been used in many epidemiologic studies for panoramic radiographs (22, 24, 27, 36–39). The possibility of comparisons among studies performed with calibrated observers makes this system attractive (40) in order to better standardize the evaluations and to allow the comparison with the result of other investigators. However, PAI was based on radiographic and histologic findings in the periapical region of maxillary incisors (25). So, the validity of its use for all tooth positions might be questionable, taking into account that the thickness of the cortical bone and the position of the root tip in relation with the cortex vary with tooth position (41). This is a limitation of the present study.

The simultaneous interpretation of the panoramic radiograph of each patient by 3 examiners was the consensus radiographic standard (42, 43). The intra- and interobserver reproducibility, evaluated by the Cohen kappa test, was moderate to strong (44). Taking into account that periapical areas of all the teeth, excluding only third molars, were radiographically evaluated, the results show the periapical status of the diabetic patients. Other studies have excluded teeth with absent or defective coronal restorations, teeth with their periradicular tissues near radiolucent anatomic structures, or RFT with inadequate root canal treatment (20). However, these exclusions necessarily alter the results and do not allow us to know the real periapical status of the subjects.

In the present study, 62.7% of diabetic patients showed AP, diagnosed as RPLs, in 1 or more teeth. Although this percentage was higher in the PCG (67.8%) compared with the GCG (50.0%), the difference was not statistically significant ($P = .13$). However, adjusting for age, sex, smoking habits, number of teeth, periodontal status, periapical status, and endodontic status as covariates, multivariate logistic regression analysis showed that the association between periapical status and HbA1c levels was marginally significant (odds ratio = 3.6, $P = .049$), with periapical status being the only significant explanatory variable. Moreover, in the final regression model, including only endodontic status, periodontal status, and periapical status as explanatory variables, periapical status became significant (odds ratio = 3.8; 95% CI, 1.1–13.0; $P = .03$).

Few studies have investigated the possible association of pulpal and periapical inflammation with the glycemic control of diabetic patients. In animal models, Iwama et al (15) evaluated the effects of type 2 diabetes on the development of periradicular lesions, suggesting that the metabolic conditions produced by type 2 diabetes enhance the development of periradicular lesions in rats. Garber et al (45) investigated the effect of hyperglycemia on pulp healing in exposed rat pulps capped with MTA and found that hyperglycemia adversely affects pulp healing in rats. Recently, Cintia et al (46) measured HbA1c in a diabetic model to investigate the effect of AP and periodontal disease on long-term glycemic control, concluding that oral infections affect glycemic conditions in diabetic rats and increase HbA1c levels in normoglycemic or diabetic rats. In human studies, Bender et al (17) reported that in poorly controlled diabetic patients periapical radiolucencies tend to develop during treatment. Chronic periapical inflammation in diabetic patients promotes a rise in blood glucose, worsening the metabolic state, and, vice versa, a high rate of asymptomatic tooth infections in diabetics exhibiting poor glycemia levels of an unclear cause is found (47). Schulze et al (48) described a case report showing a highly relevant correlation between insulin resistance and local dental inflammation of endodontic origin.

Numerous epidemiologic and clinical studies have been performed analyzing the relationship between DM, periodontal status, and the outcome of root canal treatment (11, 21, 22). Some of these studies suggest that diabetes contributes to root canal treatment failure, decreasing the retention of RFTs (3, 49, 50). Checking


<table>
<thead>
<tr>
<th>Explanatory variable</th>
<th>B</th>
<th>P value</th>
<th>Odds ratio</th>
<th>CI 95% inf limit</th>
<th>CI 95% sup limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Periodontal status</td>
<td>−1.8769</td>
<td>.0953</td>
<td>0.1531</td>
<td>0.0169</td>
<td>1.3888</td>
</tr>
<tr>
<td>Periapical status</td>
<td>1.3350</td>
<td>.0335</td>
<td>3.7999</td>
<td>1.1103</td>
<td>13.0053</td>
</tr>
<tr>
<td>Endodontic status</td>
<td>0.9966</td>
<td>.1359</td>
<td>2.7090</td>
<td>0.7309</td>
<td>10.0402</td>
</tr>
</tbody>
</table>

B, B coefficient in logistic regression; CI, confidence interval; HbA1c, glycated hemoglobin; inf, inferior; sup, superior.
Overall model fit: $\chi^2 = 8.05, P = .0454$. For periodontal status, 0 = absent periodontal disease and 1 = present periodontal disease; for periapical status, 0 = no tooth with radiolucent periapical lesion and 1 = 1 or more tooth with radiolucent periapical lesion; for endodontic status, 0 = no root-filled teeth and 1 = 1 or more root-filled teeth; and for HbA1c levels, 0 = HbA1c <6.5% and 1 = HbA1c ≥6.5%.
radiographically the healing of periapical lesions after endodontic treatment for 30 weeks, Chernaski and Ringsdorf (51) found a higher percentage of reduction of periapical radiolucencies in patients with low glucose groups. Fouad and Burleson (19) found that diabetic patients have a reduced likelihood of success of endodontic treatment in cases with preoperative periapical lesions. Lima et al. (52) has hypothesized, based on a literature review and clinical evidence, that periapical lesions in patients with DM present some particularities that affect the success rates of root canal treatment, increasing the rate of endodontic failure and persistent AP (17, 20). On the contrary, the results of the present study did not show a significant association between glycemic control in diabetic patients and the frequency of root canal treatment or radiographic endodontic failure and does not support that statement. There was no significant difference between the percentages of subjects having at least 1 RFT affected with AP in both groups (P > .05). The result of the present study is in agreement with previous reports that also found no association between persistent AP and diabetic status (21, 22, 53).

López-López et al. (22) studied the periapical and endodontic status of a sample of well-controlled type 2 diabetic patients (HbA1c = 6.6 ± 0.6) and determined that type 2 DM was significantly associated with an increased prevalence of AP and endodontic treatment but not with a higher prevalence of RFT with AP. However, in the present study, the quality of root canal filling and coronal restoration, which have been shown to be associated with the prevalence of persistent AP, have not been considered when evaluating the presence of periapical radiolucencies and could act as a confounding factor.

Although it is not the purpose of this investigation, some considerations can be made regarding the mechanisms by which periapical status and glycemic control could be associated. It has been stated that hyperglycemia, impairing collateral circulation, can cause diverse alterations in pulp and periapical structures (47, 52). High glucose levels can inhibit macrophage function, resulting in an inflammatory state that impairs host cellular proliferation and delays wound healing of pulp and periapical tissues (45). Moreover, hyperglycemia in inflammatory response can be associated with a reduction in IL-4 and osteoprotegerin (54) and an up-regulation in IL-1β, IL-6, IL-8, IL-10, tumor necrosis factor α, and the receptor activator of the nuclear factor kappa B ligand (52, 55). The up-regulation activity of differentiated osteoclast cells in hyperglycemic conditions has been shown, suggesting that hyperglycemia increases bone resorption (56).

On the other hand, the action of inflammatory mediators released in periapical inflammation is associated with the development of insulin resistance, which is influenced by genetically modified environmental factors, including decreased physical activity, poor nutrition, obesity, and infection (11, 57). AP involves activation of the broad axis of innate immunity. Lipopolysaccharide from anaerobic gram-negative bacteria causing AP, through activation of intracellular pathways on inflammatory cells, up-regulates proinflammatory cytokines (58, 59). These locally produced cytokines can move into systemic circulation (3) where they interact with free fatty acids and advanced products of glycosylation, characteristic of type 2 DM. The activation of these inflammatory pathways in immune cells (monocytes or macrophages), endothelium cells, adipocytes, hepatocytes, and muscle cells could promote an increase in the overall insulin resistance, altering the metabolic control in patients with both type 2 diabetes mellitus and chronic apical periodontitis (58, 59). Thus, it can be proposed that AP, in a similar manner to that of obesity, could initiate or propagate insulin resistance by enhancing activation of the overall systemic immune response initiated by inflammatory cytokines.

The data reported in the present study, together with the results of studies conducted so far, further support a relationship between glycemic control and periapical inflammation in diabetic patients. Clinical and prospective epidemiologic studies are needed to deepen the connection between inflammatory disease of endodontic origin and type 2 diabetes mellitus.

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References
Clinical Research


