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| ORIGINAL

Systemic conditions of diabetic patients diagnosed with apical periodontitis

Condições sistêmicas de pacientes diabéticos diagnosticados com periodontite apical

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ABSTRACT

Objective: This study aimed to evaluate the association between glycemic control status in type 2 diabetes mellitus (T2DM) patients and apical periodontitis. **Methods**: Twenty-seven patients were involved in this study. The survey was based on anamnesis, intra and extra oral examination and radiographic evaluation. Diabetes *mellitus* information involved type of diabetes and blood glucose analysis. Patients were divided according to their metabolic control status (glycemic controlled and poorly controlled T2DM patients). **Results**: A higher fasting blood glucose level ($p = 0.004$) and a higher percentage of HbA1c ($p = 0.0001$) were demonstrated in poorly controlled T2DM patients when compared to glycemic controlled T2DM. However, the frequency of apical periodontitis and the elapsed time since diabetes mellitus diagnosis were higher in controlled T2DM patients, reaching 64%. Nevertheless, controlled T2DM patients presented a higher number of apical periodontitis cases ($p < 0.05$). Findings support that controlled patients T2DM presented higher presence of apical periodontitis than poorly controlled T2DM ones. In these patients, the time elapsed since the diagnosis was higher,

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which may have provided a longer period of oscillation and/or uncontrolled metabolism. **Conclusion**: Therefore, it might contribute to the development and maintenance of apical periodontitis in glycemic controlled patients of this study.

Indexing terms: Periapical periodontitis. Diabetes Mellitus, Type 2. Glycemic control.

RESUMO

***Objetivo**: Este estudo objetivou avaliar a associação entre o estado de controle glicêmico em pacientes com diabetes mellitus tipo 2 (DM2) e a periodontite apical. **Métodos**: Vinte e sete pacientes foram envolvidos neste estudo. A pesquisa baseou-se na anamnese, exame intra e extraoral e avaliação radiográfica. As informações sobre o diabetes mellitus envolveram o tipo de diabetes e a análise da glicose sanguínea. Os pacientes foram divididos de acordo com seu estado de controle metabólico (pacientes com DM2 com controle glicêmico e pacientes com DM2 mal controlados). **Resultados**: Um maior nível de glicose em jejum (p = 0,004) e uma maior porcentagem de HbA1c (p = 0,0001) foram demonstrados em pacientes com DM2 mal controlada quando comparados com DM2 com controle glicêmico. Porém, a frequência de periodontite apical e o tempo decorrido desde o diagnóstico de diabetes mellitus foram maiores nos pacientes com DM2 controlado, chegando a 64%. No entanto, os pacientes com DM2 controlada apresentaram um maior número de casos de periodontite apical (p < 0,05). Os achados suportam que pacientes controlados com DM2 apresentam maior presença de periodontite apical do que pacientes com DM2 mal controlada. Nesses pacientes, o tempo decorrido desde o diagnóstico foi maior, o que pode ter proporcionado um período maior de oscilação e/ou metabolismo descontrolado. **Conclusão**: Portanto, pode contribuir para o desenvolvimento e manutenção da periodontite apical nos pacientes com controle glicêmico deste estudo.*

***Termos de indexação**: Periodontite apical. Diabetes Mellitus tipo 2. Controle glicêmico.*

INTRODUCTION

Diabetes Mellitus (DM) is a heterogeneous group of metabolic disorders characterized by hyperglycemia resulting from defects in insulin action, insulin secretion or both [1]. The most common form of DM is type 2 diabetes (T2DM), which affects about 90-95% of diabetes cases. This disease affects about 347 million people worldwide and is considered a public health problem, reaching about 471 million people by 2035, in which two-thirds of patients will be affected in developing countries [2]. Diabetics can also be classified according to their glycemic control, as controlled patients, or poorly controlled individuals [1-5]. Currently, DM treatment is usually based on the American Diabetes Association (ADA) recommended protocol (2015), encompassing nutritional guidance, exercise training and/or drug administration [1,2,6].

T2DM could be closely associated with several systemic complications such as nephropathy, retinopathy, microangiopathy and healing problems. Additionally, diabetes also influences oral health [1]. Chronic hyperglycemia can cause decreased salivary flow rate and/or xerostomia, burning mouth syndrome, glossodynia, taste disorders, oral mucosa ulcers, enamel hypocalcification, impaired healing, ketone breath, lichen planus and also periodontal disease [4]. Furthermore, several studies have demonstrated a direct relationship between periodontal disease and DM [4,7,8] and also a significant increase in the prevalence of apical periodontitis (AP) in diabetic patients, compared to non-diabetic patients [9-11].

Endodontic infections are caused by numerous communities of bacterial species, organized in biofilms attached to the root canals walls and evolve to pulp degradation, necrosis and periapical lesion [12-14]. Apical Periodontitis (AP) consists of an inflammatory process triggered by dental trauma or aggressive agents including microbial agents, chemical agents, and physical agents from the root canal, with consequent bone resorption [13,14]. Although periodontal disease and AP are in distinct areas, both can be considered as chronic/acute infections, sharing a common polymicrobial flora. These include predominant Gram-negative bacteria and high levels of inflammatory mediators [14,15]. In this regard, periodontal and periapical disease installation depends on inflammatory and immunopathological events.

Systemic diseases, such as DM, can modify these events and contribute to healing delay and compromised immune response, predisposing to chronic inflammation and low tissue repair capacity [11, 15-17]. The relation between DM and periapical lesions has been analyzed by many studies. Research demonstrated that after pulp exposure in diabetic rats, an inflammation of periodontal ligament, resorption of both apical root and alveolar bone were observed in higher degree in comparison with control animals [18]. Human studies regarding pathogenesis, progression, and AP healing in diabetic patients were

evaluated by Bender & Bender [19] that found a high rate of periapical lesions in diabetics with high blood glucose levels. After evaluating several reports in the literature regarding the relationship between apical periodontitis and DM, our study aimed to evaluate the metabolic and systemic conditions of patients diagnosed with apical periodontitis and type 2 diabetes (T2DM).

METHODS

Ethical aspects

The present study was based on standard ethical principles and was approved by the Ethics Committee of Universidade Católica de Brasília (protocol number 220/2011), Brazil. Fifty patients were treated at Universidade Católica de Brasília Dental School by the extension project "Interdisciplinary approach in promoting health and impact on Diabetes Mellitus patients' life quality". This interdisciplinary project promoted lectures and demonstrations about oral hygiene, nutrition, and physical activity. Of the fifty patients seen, 27 patients, with T2DM met the inclusion criteria of this research. All patients signed the informed consent form.

Inclusion and exclusion criteria

The inclusion criteria were patients diagnosed with type 2 diabetes, with medical records filled out correctly, within the age group >18 years old and diagnosed with apical periodontitis. Only patients who did fasting plasma glucose and HbA1c tests by biomedicine group in Universidade Católica de Brasília were included. Exclusion criteria corresponded to patients who did not sign the informed consent form, patients with complete dental absence and patients with absence of periapical lesions.

Study population

Personal data such as gender and age were collected. Medical history was held for investigation of systemic health, type of diabetes, diabetes duration and strategies of glycemic control (diet, insulin, drugs). Patients' data were collected based on type of diabetes. Only patients with a previous T2DM diagnosis were included [1,2,5]. Data related to capillary fasting glucose (normal <130mg.dL^{-1}), casual postprandial glucose (normal < 180mg.dL^{-1}) and glycated hemoglobin-HbA1c (normal <7%) levels were collected through tests performed by biomedicine University group. Patients with HbA1c >7% were considered as poorly controlled T2DM patients, according to ADA (2015) [1].

Extra-oral and intra-oral evaluation

Two calibrated professionals performed clinical intra-oral (periodontal, dental evaluation and analysis of the entire oral cavity), extra-oral and radiographic exams. The intra-oral exam evaluated structures and teeth needing therapeutic intervention. The radiographic exam (periapical radiography) was held in RX Pantograph Wall (GNATUS – Brazil), in Universidade Católica de Brasília. It was analyzed under a magnifying glass and light box, in order to identify apical periodontitis from radiolucent areas at endodontically compromised teeth periapex, without previous endodontic treatment. Patients included in this study had at least one tooth with an AP diagnosis [11].

Statistical analysis

According to statistical analysis, normal distribution was verified by Kolmogorov-Smirnov test. Data were described as mean and Standard Deviation (SD). The Student's t-test demonstrated differences between groups. The correlation matrix was based on Pearson's test. All data were analyzed with GraphPad Prism® (GraphPad Software, Inc., California, USA). The significance value was considered $p < 0.05$.

RESULTS

Characterization of controlled and poorly controlled T2DM patients

After a studied population general analysis, patients aged between 44 and 82 years are perceived. In the glycemic controlled T2DM patient group (n. 11; 41%), it was observed that 45% were female and 82% were older than 55 years. Seventy-three percent of these patients had been diagnosed more than 10 years previously (figure 1A and 1E). Glycemic data from these patients are provided in

table 1 and figure 1C. This group revealed a higher number of teeth with AP (64%) compared to poorly controlled T2DM patients (figure 1D – $p < 0.05$).

The poorly controlled T2DM group (n. 16; 59.0%) demonstrated 62.5% of female patients and 50.0% younger than 55 years (figure 1A). Moreover, 56.0% of these patients had been diagnosed more than 10 years previously (figure 1A). Levels of glucose are shown in Table 1 and Figure 1C. These patients revealed a higher level of fasting glucose compared to the glycemic controlled group ($p = 0.004$) (figure 1B). A higher HbA1c level in poorly controlled T2DM patients was observed ($p = 0.0001$) (figure 1C). It was also observed that the controlled T2DM group presented a higher number of AP cases and a longer time since its diagnosis, compared to poorly controlled T2DM patients (figure 1D and 1E). According to age, poorly controlled T2DM patients demonstrated a higher number of individuals aged less than 55 years. These data suggest that the poorly controlled T2DM group presents a younger population and higher glycemic levels.

In addition, assessed that all patients who had PA were diagnosed with periodontal disease, regardless of metabolic control (glycemic controlled T2DM or poorly controlled T2DM).

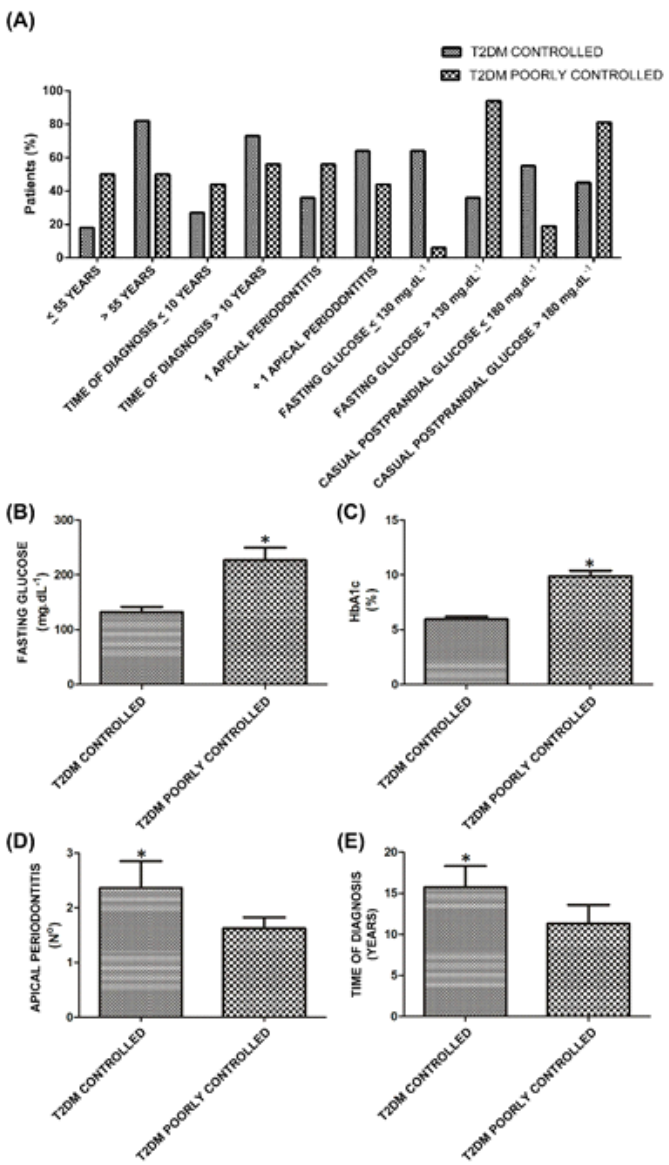

Figure 1. (A) Comparisons between glycemic controlled and poorly controlled T2DM patients. Percentage of age, time since diagnosis, prevalence of apical periodontitis and fasting glucose. (B) represents fasting glucose value between controlled and poorly controlled T2DM. (C) represents HbA1c value between controlled and poorly controlled T2DM. (D) represents the number of periapical lesions in controlled and poorly controlled T2DM. (E) represents the median time since T2DM diagnosis in controlled and poorly controlled T2DM. * Statistical differences were registered in each figure ($p < 0.05$).

Drug therapy and glycemic control

The Table 2 shows the used drugs for diabetes complications control and the DM state. Controlled and poorly controlled diabetic patients used oral hypoglycemic drugs more frequently than any other strategy for diabetes control, such as diet. Comparisons between groups revealed that poorly controlled patients demonstrated the highest frequency of treatment with insulin alone and insulin combined with oral hypoglycemic agents. Glycemic controlled T2DM patients, however, revealed a greater percentage of drugs used to treat other diseases compared to poorly controlled patients.

Correlation between controlled and poorly controlled T2DM patients

Pearson's correlation test revealed a significant relationship between fasting glucose levels and the presence of apical periodontitis ($p = 0.011$ and $r = 0.725$) in controlled T2DM patients (table 3). By contrast, the poorly controlled T2DM group demonstrated a relationship between fasting blood glucose and HbA1c ($p = 0.001$ and $r = 0.722$). In this analysis, we observed higher fasting plasma glucose related to a higher HbA1c level (table 4). The correlation matrix also demonstrated a higher level of fasting glucose related to a lower age of poorly controlled patients ($p = 0.047$

Table 1. Mean and standard deviation (SD) values of glycemic levels in controlled and poorly controlled T2DM patients with apical periodontitis. Values of *p* fasting glucose: *p*=0.02, casual postprandial glucose: *p*=0,003 and HbA1c: *p*=0.01. All patients had diagnosis of periodontal disease.

	Apical Periodontitis	
	T2DM Controlled	T2DM Poorly controlled
	Mean±SD	Mean±SD
Fasting glucose	132.36±31.01	227.03±90.77
Casual postprandial glucose	193.95±109.86	280.75±103.89
HbA1c	5.95±0.83	9.87±2.08

Table 2. Percentage of patients in distinct treatments for diabetes control.

Treatments	T2DM Controlled n (%)	T2DM Poorly controlled n (%)
Any antidiabetic drug	0 (0)	1 (6.25)
Just oral hypoglycemic	6 (54.50)	7 (43.75)
Insulin alone	0 (0)	2 (12.50)
Oral hypoglycemic and Insulin	3 (27.30)	5 (31.25)
Diet alone	2 (18.20)	1 (6.25)
Other drugs	6 (54.50)	5 (31.25)

Table 3. Data correlation between controlled T2DM patients. Correlation matrix of all the variables related to controlled T2DM patients, r value and p value were represented. * Correlation of fasting glucose and periapical disease.

	Fasting Glucose ($mg.dL^{-1}$)	Casual Postprandial Glucose ($mg.dL^{-1}$)	HbA1c (%)	Apical Periodontitis (Nº)	Age (years)	Time of diagnosis (years)
Fasting Glucose ($mg.dL^{-1}$)	1	0.4217715	0.4553661	0.7254009 *p=0.01152083	-0.2118976	0.105633
Casual Postprandial Glucose ($mg.dL^{-1}$)		1	0.5794778	0.5252199	0.2945139	0.4976579
HbA1c (%)			1	0.2854359	0.02617399	0.07070317
Apical Periodontitis (Nº)				1	-0.2615322	0.04357069
Age (years)					1	0.3389872
Time of diagnosis (years)						1

and r = -0.501) (table 4). It also revealed higher casual postprandial glucose related to a higher diabetes duration (p = 0.010 and r = 0.621) (table 4).

DISCUSSION

DM patients may present decreased resistance to infections and impaired tissue repair, contributing to increased susceptibility to infection and inflammation processes [15, 20]. Thus, regarding oral health, correlations are reported between DM and periodontal disease and between DM and AP [5,21], but the relationship between diabetes and endodontic pathologies is still poorly elucidated with controversial data.

Studies have reported that poor diabetes metabolic control may be related to AP persistence [22].

Table 4. Data correlation between poorly controlled T2DM patients. Correlation matrix of all the variables related to poorly controlled T2DM patients, r value and p value were represented. *Correlation of the variables that related in poorly controlled T2DM patients ($p < 0.05$) correlation between HbA1c and fasting glucose. **Correlation between age and fasting glucose. ***Correlation between time of diagnosis and casual postprandial glucose.

	Fasting Glucose (mg.dL^{-1})	Casual Postprandial Glucose (mg.dL^{-1})	HbA1c (%)	Apical Periodontitis (Nº)	Age (years)	Time of Diagnosis (years)
Fasting Glucose (mg.dL^{-1})	1	0.2891853	0.7226633 *p=0.00156445	-0.07303641	-0.5019669 **p=0.04756173	-0.2944087
Casual Postprandial Glucose (mg.dL^{-1})		1	0.3567923	0.07919022	-0.05713839	0.6216142 ***p=0.01015194
HbA1c (%)			1	0.1964622	-0.1797355	-0.07008956
Apical Periodontitis (Nº)				1	0.1092009	0.3343646
Age (years)					1	0.243223
Time of diagnosis (years)						1

Therefore, high glucose levels can inhibit macrophage function, impairing cell proliferation and delay the healing process of periradicular tissues [23]. The activity and regulation of osteoclast differentiation can also be altered in hyperglycemia conditions. Moreover, bone resorption is enhanced in hyperglycemia levels; according to in vitro studies [18,22,24]. However, clinical association between DM and AP remains inconclusive [25]. Since there is no scientific evidence clinical about the bidirectional relations between DM and AP [9,11].

The present study evaluated the metabolic control of patients by monitoring exams based on ADA protocols. Controlled T2DM patients are described as patients with fasting glucose ≤130mg.dL^{-1}, casual postprandial glucose ≤180 mg.dL^{-1} and HbA1c <7%. HbA1c evaluates glycemic exposure over time and provides blood glucose levels from 30 to 90 days before blood collection. The HbA1c is a gold standard to determine glycemic levels and risk for developing complications of DM [1,26].

The participants were selected from an extension project of the UCB, which aimed to treat the patient in a multidisciplinary way, involving nutrition, physiotherapy, dentistry and biomedicine evaluations and interventions. All courses making joint action to normalize metabolic condition of the patient. Therefore, the exams of fasting glucose, casual plasma glucose and glycated hemoglobin of all participants were realized on the biomedicine laboratory of the university.

Most patients from this study are older than 55 years [21,25]. Studies demonstrated that elderly people seem to be more susceptible for diabetes development [1, 2, 11]. Further evidence observed that T2DM diagnosis was more than 10 years, which is also in accordance with previous studies [8,15]. The DM development period may influence periodontal disease progression and aggressiveness, as well as AP development [14,15], depending on glycemic control levels [8,27].

There are few studies that evaluated the metabolic status of patients with apical periodontitis and T2DM. Curiously, T2DM glycemic controlled patients had a higher number of AP cases when compared to the poorly controlled group. Thus, although fasting glucose and Hb1Ac are controlled, it is possible that AP development in the controlled T2DM group may be influenced by DM evolution over time. The oscillation period and/or uncontrolled metabolism may also have contributed to this process. Thus, although the glycated hemoglobin value represents the patient level of metabolic control in the last 90-120 days, it does not inform if patient maintained a good metabolic control status since the diagnosis of the DM [1,25]. Other fact that may influence these results was the fact that the T2DM controlled patients presented elder patients and a longer time of DM diagnosis than in T2DM poorly controlled patients, allowing more time for diabetes control.

Study demonstrated that diabetic patients, even with a good metabolic control, could present a significant

increase in AP prevalence [11]. This was also observed in the present study after Pearson's correlation analysis. The present results also demonstrated a higher number of AP cases in patients that presented higher levels of fasting glucose. This evidence highlights the importance of clarifying the relationship between metabolic control and the existence/continuation of AP in T2DM patients. The time since DM diagnosis is also an important point. After DM diagnosis, an effective therapy for metabolic control must be performed. The management of diabetic patients might also involve the use of specific medications to control other diseases that may have been developed over the years if uncontrolled metabolism peaks persist.

According to poorly controlled T2DM patients (HbA1c > 7%), it was observed that individuals aged less than 55 years presented higher levels of fasting blood glucose, as demonstrated by de Almeida-Pititto et al. [28]. Our study also revealed that poorly controlled patients demonstrated higher levels of HbA1c related to higher levels of fasting blood glucose levels. This correlation was also reported previously [29]. In the same group, it was observed that the prevalence of AP was significantly lower compared to controlled patients. This finding may be related to a short period of uncontrolled metabolism, without the progression of the disease and its complications. According to the correlation matrix, the longer the time elapsed until the diagnosis of DM in poorly controlled T2DM patients, the higher the levels of casual blood glucose observed, which may contribute to the development of periodontal disease and AP in all these patients.

This study demonstrated that diabetic patients, independently of metabolic situation, showed higher prevalence of apical periodontitis, which may be associated with systemic disease itself [30]. Similar results were found by Arya et al. [31] which did not find any significant difference in healing between good controlled and poor controlled patients or those with raised HbA1c levels. Unfortunately, apical periodontitis may also be associated with the virulence of certain bacteria involved in endodontic pathology, which can be not only associated with the onset of this disease but also with the persistence of apical periodontitis [23].

Apical periodontitis happens because a process of pulp necrosis [9] and it occurs independent of the DM systemic condition [11]. However, the poorly control of metabolic variables in DM patients can aggravates the initiation and/or progression of AP. On the other hand, the initiation and/or progression of AP, may also represent an important factor of misbalance in DM patients worsening the condition [13,14].

This fact also reinforces the importance of clinical and radiographic analysis to monitor all patients after endodontic treatment, especially those with DM, and to control the onset or regression of apical periodontitis [27,32]. Analyses performed in this study were based on blood tests related to DM diagnosis, besides an accurate statistical analysis and similar numbers of patients in each group. Another important point regarding the criteria is that the study was based on the analysis of total periapical radiographs to support endodontic diagnosis.

Although our findings indicated that apical periodontitis is more pronounced in controlled diabetic patients, it is also important to point out some disadvantages of cross-sectional studies. The difficulty of investigating low-prevalence conditions, the failure to associate exposure to disease and period of investigation. Moreover, the fact that cross-sectional studies did not determine the duration of the disease could have influenced the survey data [33]. Indeed, the present study revealed the importance of metabolic control to decrease the risk of development and perpetuation of systemic and oral diseases. DM patients must be instructed about the best treatment for each case and mainly the importance of an early diagnosis. DM treatment should be based on an interdisciplinary approach, involving dentists and health professionals promoting a better quality of life for DM patients.

CONCLUSION

Based on these findings and considering study limitations, it can be concluded that patients with higher age presented more difficulty in establishing metabolic control. Moreover, the AP presence was constant in both controlled and poorly controlled groups. Nevertheless, a greater number of affected teeth was observed in glycemic controlled T2DM patients. Glycemic controlled T2DM patients also demonstrated a longer time since the DM diagnosis, and this fact could contribute to the metabolic control state in these patients. It also highlights the need to conduct more clinical and prospective epidemiological studies to better understand the relationship between endodontic inflammatory disease and DM.

Collaborators

All authors have contributed to the development of this original research. PAO SILVA and SMF LIMA were responsible for all collected data. JA ALMEIDA was involved in statistical analysis. DC GRISI and EM KOGAWA coordinated the extension project "Interdisciplinary approach in promoting health and impact on quality of life of Diabetes Mellitus patients", in Dental School of the Universidade Católica de Brasília. SC LONGATTI was responsible for performing blood tests. OL FRANCO and TMB REZENDE were involved in data analysis and in manuscript preparation.

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