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Apical lesions of endodontic origin in diabetic patients

An integrative systematic review

Stefano Cavalca

Dissertação conducente ao Grau de Mestre em Medicina Dentária (Ciclo Integrado)

—

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An integrative systematic review

Trabalho realizado sob a Orientação de
" Prof. Dr. Pedro Bernardino "

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DECLARAÇÃO DE INTEGRIDADE

Eu, acima identificado, declaro ter atuado com absoluta integridade na elaboração deste trabalho, confirmo que em todo o trabalho conducente à sua elaboração não recorri a qualquer forma de falsificação de resultados ou à prática de plágio (ato pelo qual um indivíduo, mesmo por omissão, assume a autoria do trabalho intelectual pertencente a outrem, na sua totalidade ou em partes dele). Mais declaro que todas as frases que retirei de trabalhos anteriores pertencentes a outros autores foram referenciadas ou redigidas com novas palavras, tendo neste caso colocado a citação da fonte bibliográfica.

ACKNOWLEDGMENT

I want to thank my family, my parents, my grandparents and everyone who has been by my side over the years for both economic and social support.

I also want to thank my classmates especially my colleague Edoardo Castagna for their mutual support in studying and continuing our career.

I want to dedicate this study to my grandmother Clara Tellini who died following complications brought on by diabetes.

RESUMO

INTRODUÇÃO: O diabetes mellitus (DM) é uma doença endócrina que pode afetar diversas funções do sistema imunológico do indivíduo. Nos últimos anos vários artigos correlacionam a diabetes com o aparecimento de periodontite apical (AP) ou com insucesso do tratamento endodôntico e não cicatrização da lesão apical.

OBJETIVOS: Revisar e integrar a bibliografia sobre uma possível relação entre lesões periapicais e diabetes e avaliar o sucesso de tratamentos endodônticos não cirúrgicos nestes pacientes.

MATERIAIS E MÉTODOS: Revisão sistemática integrativa com busca no PubMed.

RESULTADOS: Foram selecionados 12 artigos. 7 sobre a prevalência de AP em pacientes com DM, 3 sobre o resultado do tratamento endodôntico e 2 sobre ambos.

DISCUSSÃO: Pacientes diabéticos são mais propensos a infecções orais devido às alterações imunológicas decorrentes da doença. A hiperglicemia crônica pode ser responsável por retardar o tempo de cicatrização de uma lesão levando a uma maior probabilidade de desenvolver lesões apicais crônicas e um atraso na cicatrização após o tratamento endodôntico até mesmo falha do tratamento.

CONCLUSÃO: A diabetes mellitus parece estar associada ao aumento da prevalência de periodontite apical e com maior probabilidade de desenvolver lesões periapicais com características crônicas, mas o alto risco de bias e a presença de inúmeros artigos contraditórios sobre o assunto não nos permitem afirmar isso com absoluta certeza. O tratamento endodôntico tem menor probabilidade de sucesso em pacientes diabéticos, maior probabilidade de atrasos na cicatrização de lesões periapicais e maior probabilidade de desenvolver periodontite apical em dentes tratados endodonticamente.

Palavras-chave: Diabetes, Periapical, Apical periodontite.

ABSTRACT

INTRODUCTION: Diabetes mellitus (DM) is an endocrine disease that can affect various functions of the individual's immune system. In recent years several articles correlate diabetes with the appearance of apical periodontitis (AP) or with failure of endodontic treatment and non-healing of the apical lesion.

OBJECTIVES: Review and integrate the bibliography on a possible connection between periapical lesions and diabetes and to evaluate the success of non-surgical endodontic treatments in these patients.

MATERIALS AND METHODS: Integrative systematic review with search through PubMed.

RESULTS: 12 articles were selected. 7 on the prevalence of AP in DM patients, 3 on the outcome of endodontic treatment and 2 on both.

DISCUSSION: Diabetic patients are more prone to oral infections due to immunological alterations brought by the disease. Chronic hyperglycemia can be responsible for slowing the healing time of a lesion leading to a greater probability of developing chronic apical lesions and a delay in healing following endodontic treatment even up to treatment failure.

CONCLUSION: Diabetes mellitus seems to be associated with an increase in the prevalence of apical periodontitis and with a greater probability of developing periapical lesions with chronic characteristics, but the high risk of bias and the presence of numerous contradictory articles on the subject do not allow us to state this with absolute certainty. Endodontic treatment has a lower probability of success in diabetic patients, a greater probability of delays in the healing of periapical lesions and a greater probability of developing apical periodontitis in endodontically treated teeth.

Keywords: Diabetes, Periapical, Apical periodontitis.

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ABREVATIONS

(DM) - Diabetes mellitus.

(PL) - periapical lesions.

(AP) - Apical periodontitis.

(HbA1c) - Glycated haemoglobin A.

(RPLs) - Radiolucent periapical lesions.

(RFTs) – Root filled teeth.

(AGC) - Adequate glycemic control.

(IGC) - Inadequate glycemic control.

(ET) - Endodontic treatment.

(CBCT) - Cone beam computed tomography.

(RCT) - root canal treatment

(PAs) - periapical abscesses

(T1DM) – type 1 diabetes mellitus

(T2DM) – type 2 diabetes mellitus

(AGEs)-Advanced glycation end products

INTRODUCTION

Diabetes mellitus (DM) can be defined as a set of metabolic disorders of various etiologies, affecting carbohydrate, lipid and protein metabolism. It is considered one of the greatest public health challenges of our century and of the future, in the world affecting more than 422 million people worldwide. (1)

Diabetes can manifest itself for different reasons and in different ways because of this it has different classifications among which the main ones are type 1 diabetes, type 2 diabetes, gestational diabetes, monogenic diabetes and diabetes caused by other diseases or drugs.(2)

Among the previously indicated variants, the most common in the world population can be broadly classified into type 1 diabetes mellitus and type 2 diabetes mellitus. (2)

The type 1 diabetes, also known as insulin-dependent diabetes, or juvenile diabetes; has an idiopathic or autoimmune cause with destruction of the insulin-producing beta cells in the pancreas, leading to a deficiency of insulin secretion. Its diagnosis usually occurs in children and young adults, with normal weight or lean build, however it can also be detected at any age.

The type 2 diabetes is a complex multifactorial disease, appears mainly in elderly, overweight and adult subjects and is characterized by having peripheral insulin resistance, increased glucose production by the liver and ultimately decreased insulin secretion. Diabetes mellitus has also been associated with impaired immune responses leading to chronic inflammation, gradual tissue breakdown and decreased ability to repair.(3)

Both type 1 diabetes mellitus and type 2 diabetes have numerous possible long-term complications that can be reduced by controlling blood glucose, keeping the glycated haemoglobin A (HbA1c) keeping the levels below the maximum standard values. HbA1c values <6.5% usually indicate good control. In a non-diabetic person, HbA1c varies between 3% up to a maximum of 6%.

It has also been reported in numerous articles that the severity of the complications brought about by diabetes mellitus is inversely proportional to the glycemic index control that the patient manages to implement.(4)

Diabetes-related oral manifestations described thus far in the scientific bibliography include xerostomia, tooth decay, periodontal disease, gingivitis, oral candidiasis, burning mouth syndrome, taste disturbance, oral lichen planus, geographic tongue, fissured tongue, delayed wound healing, increased incidence of infections, salivary dysfunction, impaired eruption of teeth, altered taste, and other sensorineural disturbances. (5)

The bidirectional association between oral health and diabetes has been extensively discussed in the literature especially its association with periodontal disease. In recent years more and more in the endodontic context experimental or clinical studies are evaluating the association with a higher prevalence of periapical lesions in patients with uncontrolled glycemic index. (6)

Several articles have been written correlating diabetes with the appearance of apical or with failure of endodontic treatment and non-healing of the apical lesion.

Apical periodontitis (AP) is defined as an inflammatory process surrounding the apex of one or more of the roots of the tooth, after a microbial infection of the root canal system. (7)

The incidence of new cases of AP in the United States ranges from 27 to 41% depending on age. In Europe, the prevalence of AP reaches 34-61% of individuals, increasing with patient age. (8)

Ideally the natural healing process of an apical periodontitis should be characterized by an absence of symptoms, absence of radiographic abnormalities in the peri-root tissues and evidence of a biological seal of the root canal or by the presence of a fibrous capsule with the presence of few inflammatory cells. (9)

OBJECTIVE AND HYPOTHESIS

The aim of this study is:

- To review and integrate the bibliography on a possible connection between periapical lesions and diabetes.
- To evaluate the success of non-surgical endodontic treatments in these patients.

The null hypothesis is that diabetes does not influence the appearance of periapical lesions of endodontic origin, treatment and healing.

MATERIAL AND METHODS

This study answers the following clinical questions of the PICO model:

P	**Population**	Patients with diabetes
I	**Intervention**	Patients with a periapical lesion of endodontic origin
C	**Control**	Patients without diabetes
O	**Outcome**	Association of apical lesion to patients with diabetes and outcome of endodontic treatment

PICO table

The study also attempts to answer the following questions:

- Is there a greater probability of developing an apical lesion in diabetic patients?
- Does endodontic treatment have the same probability of success in these patients?

1. Identification methodology

A literature search was performed using the PubMed® search engine in the MEDLINE® database. using the following combination of keywords (diabetes) AND (periapical). Articles dealing with the association between periapical lesions of endodontic origin in diabetic patients or with the healing of periapical lesions after a endodontic treatment published between January 2013 and February 2023 were included.

2. Screening

The screening phase was divided into 3 parts following the PRISMA model (Preferred Reporting Items for Systematic and Meta-Analyses). After identification the articles went through the first phase of screening through the reading and analysis of the title and the abstract to select those relevant to the topic. The articles needed to respond to the outcome of this study which is association of apical lesion to in patients with diabetes and outcome of endodontic treatment. During the second phase, the complete article available in electronic form was read and analysed, excluding any publications made for the same author, which presented any conflict of interest on the part of the authors, or which presented evident bias.

During the third phase, articles that did not meet the eligibility criteria used in the study were excluded. The articles that did not pass the screening phase due to the lack of some eligibility criteria, specifically due to being systematic reviews, meta-analyses or case reports were used for the realization of the introduction and discussion of the results.

3. Eligibility criteria

Inclusion and exclusion criteria were the following:

INCLUSION	EXCLUSION
Articles published in the last 10 years.	Articles published before 2013 were excluded.
Articles in any language.	Articles not related to with the topic.
Studies investigating the possibility association periapical lesions of endodontic origin and diabetes.	Literature reviews, meta-analysis and systematic review
Studies on the outcome of endodontic treatment in diabetic patients.	Articles whose full text was not accessible
Retrospective, prospective clinical studies.	in vitro or animal studies.

4. Supplementary bibliography

A total of fifteen supplementary studies were used for the introduction of the study and discussion of the results. The supplementary studies used in this integrative systematic review are those that did not pass the selection criteria due to the type of study (systematic reviews, case reports) or articles selected through a free manual.

5. Flow chart

The methodology of the study leads to the following flow chart.

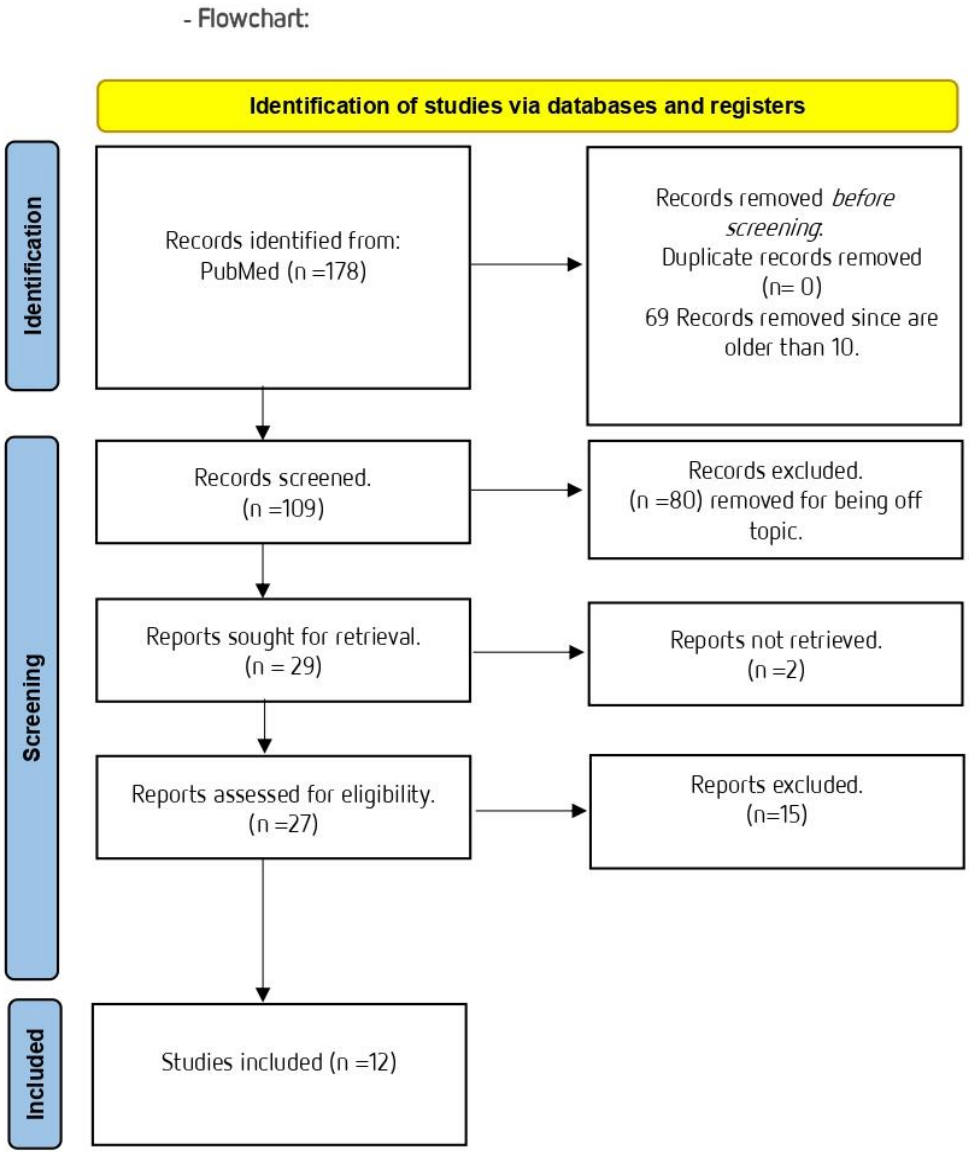

Figure 1

RESULTS

The articles analysed all come from the Pubmed® system, the first search led us to find 178 articles, of which only 12 were selected following the above methodology.

The selected articles were then divided into three tables:

1. The first general in which all twelve articles selected have been reported in chronological order of publication.
2. The second one reporting the articles and the respective conclusions on the appearance of periapical lesions in diabetic patients before performing the endodontic treatment on the affected tooth.
3. The third reporting the articles and the respective conclusions on the success of endodontic treatment and the healing after the treatment in diabetic patients.
4.

1. Table general

Title and year of publication	Objective	Type of study and method	Population	Results	Conclusion
Diabetes Mellitus and its Influence on the Success of Endodontic Treatment: A Retrospective Clinical Study (Ferreira et al., 2014.)(10)	The aim of this study is to evaluate the influence of diabetes mellitus at the periapical tissues and the success of endodontic treatment in these patients.	Retrospective clinical study. The evaluation of the periradicular tissues was carried out using panoramic radiographs and, in the case of teeth already undergoing endodontic treatment, this analysis was based on the retro-alveolar radiographic examination carried out in the control visit.	737 cases which were made nonsurgical endodontic. treatments, between the years 2003 and 2012. Of these were selected 32 patients DM Patients were from Coimbra. Portugal	The success of endodontic treatment was 62% in patient with DM and 80% in the control group. ($p > 0.05$).	The results of this study are inconclusive regarding the increasing prevalence of apical periodontitis in diabetic patients. Regarding the evaluation of the success of endodontic treatments examined it was found that the success rate in diabetic patients is lower, though not statistically significant.

Frequency of odontogenic periradicular lesions in diabetic patients (Mesgarani et al., 2014.)(11)	The aim of this study was to evaluate the frequency of periradicular lesions in diabetic patients.	Retrospective clinical study. For all the patients, panoramic and periapical radiography were performed for the presence of any radicular radiolucent lesions. Vitality test has been done for the recorded teeth except for the root treated ones and lesions of non-endodontic origin.	134 patients with DM type II were selected. The mean age of these patient's (100 females, 34 males) was 48.85±7.14 years. Patients were from Babol, North of Iran.	Was found that the frequency of the periradicular lesions with pulp origins in diabetic patients was 90.4%.	The results show that the frequency of periradicular lesions in diabetic patients is higher in long-term diabetic patients than the short-term diabetic patients.
Glycated Hemoglobin Levels and Prevalence of Apical Periodontitis in Type 2 Diabetic Patients (Sánchez-Domínguez et al., 2015)(12)	The purpose of this investigation was to study the possible association between the prevalence of AP and the glycemic control of type 2 diabetic patients.	Cross-sectional study. The radiographic records of type 2 diabetic patients were examined. Glycemic control was assessed by the mean glycated hemoglobin (HbA1c level). AP was diagnosed as RPLs using the periapical index score.	83 type 2 DM patients were examined at the University of Barcelona dental clinic.	The prevalence of RPLs in RFT (29.6%) was similar in the group with AGC compared with the group with IGC. The analysis showed that worse periapical status correlated significantly with HbA1c levels >6.5% in type 2 diabetic patients.	HbA1c levels of diabetic patients are associated with periapical status.

Periapical healing outcome following single visit endodontic treatment in patients with type 2 diabetes mellitus (Rudranaik et al., 2016)(13)	The study aims at evaluating the clinical and radiographic healing outcome of single visit endodontic treatment, in type 2 DM patients with periapical disease.	Prospective clinical study. Diagnosis of apical periodontitis was done by clinical and radiographic examination. Pre-operative assessment of periapical status which included pain, apical tenderness & sinus tract was done.	80 patients with periapical disease were divided into 2 groups of 40 each: Group I, Control subjects and Group II, Type 2 DM. Patients were analysed by Hospital Hassan India.	Group 2 subjects had chronic and exacerbating lesions with significantly larger lesions (p=0.029). 100 % clinical healing outcome in diabetic group was seen in two months. Group 2 showed 85% success in one year on radiographic evaluation.	Type 2 diabetics had chronic and larger sized lesions when compared to control subjects. The endodontic treatment of periapical lesions in patients with poor diabetic control showed failure. The clinical and radiographic healing outcome of single visit endodontic therapy was delayed in diabetic patients.
The relationship between periapical lesions and the serum levels of glycosylated hemoglobin and C-reactive protein in type 2 diabetic patients (Al-Zahrani et al., 2017)(3)	To investigate the relationship between the presence of periapical lesions (PL) and levels of glycosylated hemoglobin (HbA1c), and C-reactive protein in patients with type 2 diabetes.	Cross-sectional study. Dental and periodontal examinations were conducted, and blood samples were obtained to determine levels of HbA1c and CRP. The presence of PL was recorded from panoramic and periapical radiographs.	100 patients with DM who satisfied the inclusion/exclusion criteria were included. Patients were from Jeddah, Kingdom of Saudi Arabia.	14% had no periapical lesions, whereas 25% had 1 or 2 lesions, 32% had 3 or 4 lesions, and 29% had 5 or more periapical lesions.	Periapical lesions are associated with a poorer glycemic control and a higher C-reactive protein level in type 2 diabetic patients.

Apical Periodontitis and Endodontic Treatment in Patients with Type II Diabetes Mellitus: Comparative Cross-sectional Survey (Smadi, 2017)(14)	The aims of this study were to investigate the prevalence of AP in DM patients compared with nondiabetic patients and to examine the effect of glycemic control on the prevalence of AP.	Comparative Cross-sectional Survey. Radiographs of a group of DM patients were compared with those of a matched nondiabetic group to identify AP. The diabetic group was subdivided according to the level of glycemic control into two subgroups: A well-controlled DM and a poorly controlled DM.	142 diabetics agreed to participate in the study were enrolled in group I. 146 nondiabetic patients were enrolled in group II. Patients were from Amman, Jordan	The prevalence of AP was higher in diabetic group than in the nondiabetic (13.5 vs 11.9%). Diabetic group had more teeth with ET compared with nondiabetic (4.18 vs 1.82%); IGC DM group had a higher prevalence of AP lesions compared with the AGC DM group (18.29 vs 9.21%).	This survey demonstrates a higher prevalence of AP in DM patients compared with nondiabetic, with an increased prevalence of persistent chronic AP. Compared with a well-controlled diabetic group, a poor glycemic control may be associated with a higher prevalence of AP and increased rate of endodontic failures.
Healing of Apical Periodontitis after Nonsurgical Treatment in Patients with Type 2 Diabetes (Arya et al., 2017)(15)	The purpose of this prospective study was to compare the success of primary root canal treatment between type 2 diabetic and nondiabetic patients and to investigate the effect of periapical healing on HbA1c in type 2 diabetic patients with apical periodontitis.	Prospective study. Sixty mandibular molars with necrotic pulps and apical radiolucency (size ≥ 2 mm X 2 mm) were included in the study. Based on the HbA1c levels, patients were divided into 2 groups: type 2 diabetic (HbA1c > 6.5%) and nondiabetic (HbA1c <6.5%). Forty-six teeth were evaluated at the 12-month follow-up.	30 patients with DM type II and 30 without DM were selected whose age is between the ages of 30 and 65 years. Patients were from Rohtak, India.	Significantly less periapical healing was observed in the diabetic group (43%) compared with the nondiabetic group (80%) at the 12-month follow-up ($P < 0.05$).	Diabetes mellitus may have a negative impact on the outcome of endodontic treatment in terms. of periapical healing. Nonsurgical endodontic treatment did not improve HbA1c levels in patients with type 2 diabetes.

Evaluation of the Relationship between Type II Diabetes Mellitus and the Prevalence of Apical Periodontitis in Root-Filled Teeth Using Cone Beam Computed Tomography: An Observational Cross-Sectional Study (Sisli, 2019)(16)	This study aimed to investigate the prevalence of AP in patients with type II DM with either AGC or IGC compared with nondiabetics using CBCT.	Observational Cross-Sectional Study. A possible association between type II diabetes mellitus and apical periodontitis was evaluated in this study using cone beam computed tomographic images of adequately root-filled and restored teeth.	29 females, 14 males were compared with a control group consisting of 162 teeth of 86 nondiabetics (56 females, 30 males). Patients were from Adana, Turkey.	The frequency of AP was 37.3% for the DM group and 28.4% for the control group, there was no significant difference between the DM group and the control group in terms of age, gender, and type of teeth evaluated.	The prevalence of AP and severe bone destruction in periapical tissues was significantly higher in the DM patients compared with the nondiabetic patients.
Apical periodontitis and glycemic control in type 2 diabetic patients: Cross-sectional study (Pérez-Losada FL et al. 2020)(17)	The objective of this study was to analyze the possible relationship between the glycemic control and the prevalence of apical periodontitis in type 2 diabetic patients.	Cross-sectional study. the radiographic records of type 2 diabetic patients were examined. HbA1c was used to assess glycemic control, considering an HbA1c level < 6.5% as well-controlled diabetes. Apical periodontitis was diagnosed as radiolucent periapical lesions using the periapical index score.	The radiographic records of 216 type 2 diabetic patients (65.0 ± 10.7 years), 117 men (54.2%) and women (45.8%), were examined. Patients were from Sevilla, Spain.	44% of diabetics had apical periodontitis, 12.5% had root-filled teeth, and 52.3% had root filled teeth with radiolucent periapical lesions.	The results reveal no association of glycemic control with the prevalence of apical periodontitis or root canal treatment in diabetic patients.

Root Canal Treatment and Apical Periodontitis in a Brazilian Population with Type 1 Diabetes Mellitus: A Cross-sectional Paired Study (Limeira et al., 2020)(18)	The aim of the present study was to radiographically investigate the prevalence of RCT and AP in type 1 DM and nondiabetic individuals and its association with history and the status of type 1 DM.	Cross-sectional Paired Study. the radiographic records of individuals with T1DM and sex-matched nondiabetic subjects were examined. The presence of RCT and AP was evaluated. Information regarding the history and the status of T1DM was collected from the medical records of each patient.	The radiographic records of 50 individuals with type 1 DM and 100 without DM were examined. The treatments were performed at the local university hospital of the Federal University of Campina Grand, Brazil.	One or more RCTs were found in 76% and 44% of diabetic and nondiabetic subjects, respectively.	RCT, AP, and RCT with AP were more prevalent in individuals with T1DM than in nondiabetic individuals. RCT and AP were associated with the presence of type 1 DM.
Diabetes Mellitus and Periapical Abscess: A Cross-sectional Study (Saleh et al., 2020)(19)	The purpose of this study was to investigate the occurrence of Pas in type 1 DM patients, type 2 DM patients, and nondiabetics in a hospital-based population.	Was conducted a cross-sectional study by accessing the University of Florida Health Integrated Data Repository, and diagnoses of T1DM, T2DM, and PA were obtained from queries using the International Statistical Classification of Diseases, 10th Revision. The following parameters were recorded: age, sex, and race.	Among 867,526 patients, we found 5260 (0.6%) with T1DM and 52,493 (6.1%) with T2DM. The treatments were performed at the University of Florida, Florida, U.S.	The prevalence of PAs in the total hospital population was 0.6%, 1% with T1DM and 6% with T2DM. In subjects without PDs, diabetic patients are almost 3 times likely to have PAs compared with nondiabetic subjects.	A higher prevalence of PAs was reported in diabetic patients compared with the other hospital population.

Impairment of the angiogenic process may contribute to lower success rate of endodontic treatments in diabetes mellitus (Martinho et al., 2021)(20)	The purpose of this study is to investigate the association between root canal treatment outcome, diabetes mellitus, and alterations of the angiogenic process.	Retrospective observational study. study was conducted in healthy (control group) and diabetic (T2DM) patients after root canal treatment. The follow-up appointments were performed to observe symptoms, the healing of periapical lesions, and the quality of root filling clinically and radiographically.	The sample consisted of 93 patients, of whom 46 were diabetic, and 47 were non-diabetic. mean age 59.4. Patients were from Coimbra, Portugal.	The assessment of the outcome of root canal treatment revealed a significant reduction in DM group comparing with control group (89.4% in control group vs 47.8% in DM group; p=0.018)	Diabetes mellitus should be considered as an important factor in the prognosis of root canal treatment and its outcomes over time.

2. Table prevalence of AP in DM patients

Author	Conclusion	
Ferreira et al., 2014 (10)	Inconclusive.	
Mesgarani et al., 2014. (11)	Higher frequency of periradicular lesions in long time diabetic patients.	
Sánchez-Domínguez et al., 2015 (12)	Higher prevalence of AP in diabetic patient.	
Al-Zahrani et al., 2017 (3)	Periapical lesions are associated with a poorer glycemic control.	
Smadi, 2017 (14)	Higher prevalence of AP in DM patients compared with nondiabetic.	
Sisli, 2019 (16)	The prevalence of AP was significantly higher in the DM patients.	
Pérez-Losada FL et al. 2020 (17)	No association between AP and DM	
Limeira et al., 2020 (18)	AP were associated with the presence of type 1 DM.	
Saleh et al., 2020 (19)	A higher prevalence of AP was reported in diabetic patients	

3. Table outcome of endodontic treatment

Author	Outcome of endodontic treatment	
Ferreira et al., 2014 (10)	Lower success rate in diabetic patients	
Rudranaik et al., 2016 (13)	Patients with poor diabetic control showed failure.	
Smadi, 2017 (14)	Increased rate of endodontic failures.	
Arya et al., 2017 (15)	Negative impact on the outcome in terms of periapical healing.	
Martinho et al., 2021)(20)	Significant reduction of success rate in DM patients	

DISCUSSION

Premises

The association between diabetes mellitus and apical periodontitis was initially proposed by Bender et al. (1963) since then countless studies have been carried out linking diabetes to various oral pathologies or vice versa correlating oral inflammation to a worsening of the ability to control diabetes mellitus. (21)

The bacterial infection that causes apical periodontitis can have various origins: periodontal, endodontic and mixed. This review only considers the endodontic origin to evaluate a possible connection with diabetes.

To be affected by an apical periodontitis of endodontic origin for the most part it is first necessary to develop a caries that reaches the vital pulp of the tooth and consequently the development of the infection also through the canals of the tooth until it reaches the apex. Carious lesions are generally considered by the world literature a multifactorial disease due to the number of variables that can increase a person's susceptibility to this disease and then cause its appearance. Carious lesions are essentially caused by the metabolism of bacteria present in the oral cavity which, by producing acidic substances deriving from fermentation, cause the gradual erosion of the enamel and over time, if treatment or a change in oral hygiene habits is not carried out by the patient, they reach dentin and pulp. Among the variables that can increase susceptibility to this disease, the main and most important that we can list are: poor oral hygiene on the part of the patient, conformation of the teeth, an incorrect diet rich in sugars and a poor salivary flow. (22)

The saliva, due to the action of the bicarbonates contained in it, provides a buffer system against both food acids and those of bacterial origin, moreover it has a mild antibacterial effect, favoured by the presence of thiocyanates, hydrogen peroxide, glycoproteins, immunoglobulins and especially lysozyme which helps in part to reduce the formation of bacteria that unbalance the oral flora.

The correlation between the presence of diabetes and xerostomia has been treated by several authors either caused by the diabetes itself or due to polymedication which many people with DM and other pathologies are subjected. Consequently, missing or having a

dysfunction of one of the most important protections that our body provides us against the development of carious lesions allows us to draw the conclusion that from a theoretical point of view the DM increases the susceptibility to carious lesions. (22)

De Lima et al. In 2020, in their systematic review with meta-analysis stated a higher frequency of development of carious lesions in diabetic patients compared to non-diabetic patients for various factors including decreased salivary flow or increased intake of glucose in diabetic patients with uncontrolled diabetes. (22)

The literature therefore shows us that some risk factors and premises for the development of apical periodontitis are encountered more frequently in diabetic patients and in those with poor glycemic control and poor medical supervision.

Diabetes mellitus as a risk factor for apical periodontitis

The data provided by the articles analysed show a higher frequency of development of apical periodontitis or of a recurrence after endodontic treatment in patients with diabetes mellitus, however it is difficult to state with certainty a causal correlation between diabetes and the first appearance of apical periodontitis due the number of variables involved in causing the development of the disease that are not always fully described and evaluated within the studies both due to the collaboration of the patients and the intrinsic difficulty in collecting data and evaluating them.

One of the most important and often not considered data is the patient's eating habits since the relationship between an excessively carbohydrate-based diet could correlate both with the development of caries and with the subsequent development of diabetes caused by peripheral insulin resistance, therefore, to type 2 diabetes. (18)

This could by itself explain the greater presence of cases of apical periodontitis in patients with uncontrolled diabetes mellitus and cause bias in the studies, in fact people subject to control of diabetes and consequently also of dietary habits and subject to greater clinical monitoring show percentages equal or even lower of apical periodontitis than in healthy patients.

In many articles analysed, the difference in the prevalence of AP can be explained by the low socio-economic level of the population studied and by the general unsatisfactory oral status due to poor oral hygiene which causes a high incidence of caries lesions and low quality of treatments achieved in addition to a low priority in general for the state of health, which makes it even more difficult to interpret the results which are very often statistically insignificant and not sufficient to correlate DM to the development of AP.

The relationship between decreased salivary flow and DM could play an important role in the development of caries and promote oral infections especially *Candida albicans* often found within root canals in diabetic patients. (23)

Furthermore, diabetic patients are more likely to be subject to the use of multiple medications, many of which can cause dry mouth, this factor could partly explain a greater development of caries and consequently AP. (22)

It should also be considered that diabetes mellitus has a direct effect on dental pulp integrity, and poor glycemic control could negatively affect this relationship. Hyperglycemia can cause various changes in pulpal structures mainly due to impaired collateral circulation, which leads to an increased risk of pupal necrosis. (6)

In addition to toothache and an occasional tendency to pulp necrosis caused by ischemia, the disease can cause structural changes in the pulp tissue such as decreased collagen concentration, increased thickness of the basement membrane of blood vessels, angiopathy, increased frequency of calcifications and endarteritis obliterans. (6)

Diabetes mellitus can also influence the periapical state through some mechanisms: altered innate immunity, hyperglycemia and irreversible formation of glycated proteins that form advanced glycation end products (AGEs), thus predisposing to a state of chronic apical inflammation by decreasing the ability to repair of periapical tissues by increasing susceptibility to infection and delaying healing, thereby increasing the prevalence of chronic apical periodontitis. (24)

The effects of diabetes mellitus on the periapical tissues and on the development of periodontitis can be summarized by the scheme made by Segura-Egea, Martín-González and Castellanos-Cosano in their systematic review published in 2015. (24)

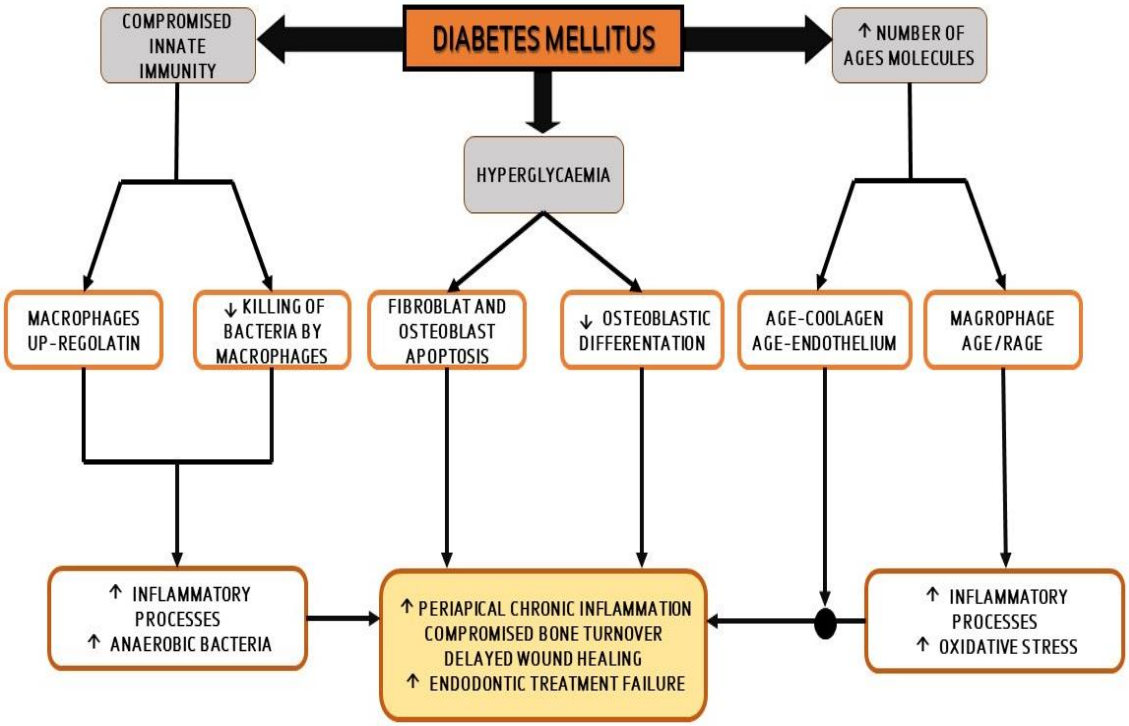

Figure 2

(Segura-Egea, Martín-González and Castellanos-Cosano, 2015,) (24)

Furthermore, diabetic patients have a more virulent and pathogenic microflora among which bacteria such as: *Fusobacterium nucleatum, Peptostreptococcus micros, Streptococcus spp* and *Eubacterium infirmum* have been identified in greater quantities than patients without diabetes mellitus. (15)

The data from the available literature and from the studies analysed suggest an association between DM and the prevalence of AP but nevertheless do not allow us to definitively conclude the existence of a close relationship between the two due to the high risk of bias to which a large part of the studies analysed are subject and in the presence of many conflicting studies.

Influence of apical periodontitis on HbAc1 level

Several studies have shown that inflammation of the oral tissues also plays a very important role in the control of the glycemic index, therefore, chronic periapical inflammation could induce or perpetuate a high chronic systemic inflammatory state, contributing to the increase in resistance to insulin and poor glycemic control. (25)

The action of inflammatory mediators released in periapical inflammation could be associated with the development of insulin resistance, together with influence from genetic and environmental factors, reduced physical activity, poor diet, obesity and further infections. (24)

Although periapical infections elicit a variety of local tissue responses to limit the spread of infection, apical periodontitis can also have systemic repercussions. Interaction between lipopolysaccharide of anaerobic gram-negative bacteria, which cause apical periodontitis, with Toll-like receptor 4 (TLR4) on macrophages and neutrophils activates the broad axis of innate immunity, increasing proinflammatory cytokines such as IL-1b, IL-6, IL-8, TNF-α and prostaglandin E2 (PGE2). These cytokines can be released into the systemic circulation inducing or perpetuating elevated chronic systemic inflammation. (4)

The influence on HbAc1 level and the development of insulin resistance could correlate with the size of the periapical lesions, their chronicity and the presence of any related systemic symptoms. (4)

Currently, the data showing improvements in the glycemic level after endodontic treatment do not seem sufficient and are often contradictory to conclude its capabilities on glycated control in patients with diabetes mellitus. (4)

Effects of diabetes mellitus on the results of endodontic treatment

In 1994 the European Society of Endodontics established as success criteria of endodontic therapy: the absence of pain, swelling and fistula, maintenance of the tooth in function as well as radiographic evidence of the normal periodontal ligament space, absence of apical periodontitis and root resorptions.

There are many therapeutic factors that can influence the results of endodontic treatment:

- First in importance is the biochemical preparation of the root canal system of the tooth. Root canal shaping is an important step in endodontic therapy to achieve apical healing and cleaning and shaping of the root canal system. However, the complex anatomy of the root canal, associated with the presence of curvatures and branches, the shape and position of the apical foramina, can interfere and hinder the shaping and cleaning of the root canal.(9)

- The type of irrigant used during preparation is critical and greatly affects the outcome of the treatment as it provides not only lubrication to the instruments used or the removal of dentinal debris but can also provide a means of killing the bacteria involved in the infection which often are unattainable with mechanical treatment alone.(9)

- The type of obturation materials used and the technique used to obtain a complete closure of the communication between the root canal and the periapical tissue. An ideal root canal sealant must have adequate physical, chemical and biological properties. Several factors can influence the success of the treatment, including the type and composition of the sealant used. The presence and release of substances from sealants can cause various reactions in contact with tissue, promoting or delaying healing.(9)

- The position of the apical limit of the obturation also plays an important role with the results of the treatment.(9)

- The last and important factor in the prognosis of treatment may be systemic diseases involving the patient's health.(9)

In diabetic patients the glucose level plays a fundamental role in immune function and healing by influencing various metabolic and cellular changes, among which we can list that:

High glucose levels can inhibit macrophage function resulting in an inflammatory situation that impairs cell proliferation and wound healing.

Hyperglycemia may be associated with reduction in IL-4, osteoprotegerin, up-regulation in IL-1b, IL-6, IL-8, IL-10, tumour necrosis factor A, and nuclear factor kappa B receptor activator ligand, all this also leads to an up-regulation of osteoclast differentiation by increasing bone resorption.(12)

In addition, it causes a decrease in osteoblast formation thus influencing bone regeneration (studies suggest that the balance between resorption and new bone deposition could be related more to the number of cells active in the process than to the individual ability to carry out their work properly).

The consequences of hyperglycemia on cell regeneration, vitamin D metabolism, differentiation and function of various cells due to glycosylation of proteins and DNA, metabolic changes in cells and activation of protein kinase C cause excretion acceleration of calcium through the urine and therefore decreasing its systemic availability and lower bone recalcification capacity.(26)

AGEs have also been shown to modify bone metabolism, increasing bone resorption and reducing osteogenesis and, consequently, bone formation.(1)(15)

Diabetes mellitus promotes fibroblast apoptosis, inhibition of collagen fibril formation and interferes with collagen cross-linking which can impair matrix protein degradation and subsequent tissue remodelling.

All this leads to a delay in the healing of the periapical tissues and to a decrease in the success rate of endodontic treatment in diabetic patients, as the articles analysed in the

results largely agree, leading to an increase in the number of cases of apical periodontitis found after endodontic treatment in diabetic patients.

Many studies such as the one performed by Gupta et al., 2020 in their systematic review with meta-analysis conclude that there is a strong connection between the endodontic outcome in terms of the presence of periapical radiolucency in teeth with root filling and diabetes mellitus. (2)

The study carried out by Arya et al., 2017 quantifies the difference in the percentage of endodontic success in patients with diabetes mellitus around 10% less than in healthy patients. (15)

Cabanillas-Balsera et al., 2019 concludes that the retention of endodontically treated teeth is much lower in patients suffering from diabetes, however for this statement it is also necessary to evaluate the enormous influence that diabetes has on periodontitis.

In fact, one of the chronic complications of diabetes mellitus is microangiopathy, which leads to a decrease in blood flow and therefore to a lower supply of nutrients and oxygen to the periodontal tissues, facilitating the progression of periodontitis, the loss of support, the increase of periodontal pockets, mobility and a poorer response to periodontal treatment. (7)

In relation to therapeutic possibilities and research points, we can note that vitamin D could have an important biological effect on glucose control, favoring the response to insulin.

Vitamin D can also influence the level of alveolar bone regeneration and the inflammatory reactions of periradicular technicians. A study on this issue concluded that vitamin D may be a potent therapeutic agent for endodontic intervention in diabetics. (27)

New studies on this mechanism are needed, a possible addition to the therapeutic procedure in patients with diabetes mellitus who require endodontic treatment.

Limitations of the study

This study is subject to the limitations given by the selected articles such as: the different diagnostic criteria used to evaluate possible apical lesions, the different tools used for the diagnosis (periapical x-rays, orthopantomography, CBCT) and the ability to define radiographic images as well as the interpretation of the same by the researchers and by the different populations analysed, socio-economic conditions and access to medical care.
Furthermore, it is subject to informational search limitations due to the accessibility of full articles in digital format, and the difficulty of searching for them through digital search engines only.
Many of the available articles focus their studies on small population numbers often not sufficient to draw statistically significant conclusions considering all the factors necessary for the correct evaluation of the effects of diabetes on the development of apical periodontitis, thus being forced to an analysis without considering some factors such as the nutrition and socioeconomic status of the people participating in the study causing an increased risk of bias in their conclusions.

CONCLUSION

Diabetes mellitus seems to be associated with an increase in the prevalence of apical periodontitis and with a greater probability of developing periapical lesions with chronic characteristics, but the high risk of bias and the presence of numerous contradictory articles on the subject do not allow us to state this with absolute certainty.

The studies analysed allow us to state that endodontic treatment has a lower probability of success in diabetic patients, a greater probability of delays in the healing of periapical lesions and a greater probability of developing apical periodontitis in endodontically treated teeth.

For the above considerations the null hypothesis that diabetes mellitus does not influence the appearance of periapical lesions of endodontic origin, treatment and healing is rejected.

Further research on the prevalence of apical periodontitis in diabetic patients is recommended, paying particular attention to patients' eating habits and on the use of vitamin D as a therapeutic support to endodontic treatment in diabetic patients.

BIBLIOGRAPHY

1. Ríos-Osorio N, Muñoz-Alvear HD, Montoya Cañón S, Restrepo-Mendez S, Aguilera-Rojas SE, Jiménez-Peña O, García-Perdomo HA. Association between type 2 diabetes mellitus and the evolution of endodontic pathology. Quintessence Int. 2020;51(2):100-107.
2. Gupta A, Aggarwal V, Mehta N, Abraham D, Singh A. Diabetes mellitus and the healing of periapical lesions in root filled teeth: a systematic review and meta-analysis. Int Endod J. 2020 Nov;53(11):1472-1484.
3. Al-Zahrani MS, Abozor BM, Zawawi KH. The relationship between periapical lesions and the serum levels of glycosylated hemoglobin and C-reactive protein in type 2 diabetic patients. Saudi Med J. 2017 Jan;38(1):36-40.
4. Mauri-Obradors E, Estrugo-Devesa A, Jané-Salas E, Viñas M, López-López J. Oral manifestations of Diabetes Mellitus. A systematic review. Med Oral Patol Oral Cir Bucal. 2017 Sep 1;22(5):e586-e594.
5. Borgnakke WS, Genco RJ, Eke PI, Taylor GW. Oral Health and Diabetes. In: Cowie CC, Casagrande SS, Menke A, Cissell MA, Eberhardt MS, Meigs JB, Gregg EW, Knowler WC, Barrett-Connor E, Becker DJ, Brancati FL, Boyko EJ, Herman WH, Howard BV, Narayan KMV, Rewers M, Fradkin JE, editors. Diabetes in America. 3rd ed. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases (US); 2018 Aug. CHAPTER 31.
6. Lima SM, Grisi DC, Kogawa EM, Franco OL, Peixoto VC, Gonçalves-Júnior JF, Arruda MP, Rezende TM. Diabetes mellitus and inflammatory pulpal and periapical disease: a review. Int Endod J. 2013 Aug;46(8):700-9.
7. Cabanillas-Balsera D, Martín-González J, Montero-Miralles P, Sánchez-Domínguez B, Jiménez-Sánchez MC, Segura-Egea JJ. Association between diabetes and nonretention of root filled teeth: a systematic review and meta-analysis. Int Endod J. 2019 Mar;52(3):297-306.
8. Segura-Egea JJ, Martín-González J, Cabanillas-Balsera D, Fouad AF, Velasco-Ortega E, López-López J. Association between diabetes and the prevalence of radiolucent periapical lesions in root-filled teeth: systematic review and meta-analysis. Clin Oral Investig. 2016 Jul;20(6):1133-41.

9. Holland R, Gomes JE Filho, Cintra LTA, Queiroz ÍOA, Estrela C. Factors affecting the periapical healing process of endodontically treated teeth. J Appl Oral Sci. 2017 Sep-Oct;25(5):465-476.
10. Ferreira MM, Carrilho E, Carrilho F. Diabetes mellitus e sua influência no sucesso do tratamento endodôntico: um estudo clínico retrospetivo [Diabetes mellitus and its influence on the success of endodontic treatment: a retrospective clinical study]. Acta Med Port. 2014 Jan-Feb;27(1):15-22.
11. Mesgarani A, Haghanifar S, Eshkevari N, Ehsani M, Khafri S, Nafarzade S, Damankesh Z. Frequency of odontogenic periradicular lesions in diabetic patients. Caspian J Intern Med. 2014 Winter;5(1):22-5.
12. Sánchez-Domínguez B, López-López J, Jané-Salas E, Castellanos-Cosano L, Velasco-Ortega E, Segura-Egea JJ. Glycated hemoglobin levels and prevalence of apical periodontitis in type 2 diabetic patients. J Endod. 2015 May;41(5):601-6.
13. Rudranaik S, Nayak M, Babshet M. Periapical healing outcome following single visit endodontic treatment in patients with type 2 diabetes mellitus. J Clin Exp Dent. 2016 Dec 1;8(5):e498-e504.
14. Smadi L. Apical Periodontitis and Endodontic Treatment in Patients with Type II Diabetes Mellitus: Comparative Cross-sectional Survey. J Contemp Dent Pract. 2017 May 1;18(5):358-362.
15. Arya S, Duhan J, Tewari S, Sangwan P, Ghalaut V, Aggarwal S. Healing of Apical Periodontitis after Nonsurgical Treatment in Patients with Type 2 Diabetes. J Endod. 2017 Oct;43(10):1623-1627.
16. Sisli SN. Evaluation of the Relationship between Type II Diabetes Mellitus and the Prevalence of Apical Periodontitis in Root-Filled Teeth Using Cone Beam Computed Tomography: An Observational Cross-Sectional Study. Med Princ Pract. 2019;28(6):533-538.
17. Pérez-Losada FL, López-López J, Martín-González J, Jané-Salas E, Segura-Egea JJ, Estrugo-Devesa A. Apical periodontitis and glycemic control in type 2 diabetic patients: Cross-sectional study. J Clin Exp Dent. 2020 Oct 1;12(10):e964-e971.
18. Limeira FIR, Arantes DC, de Souza Oliveira C, de Melo DP, Magalhães CS, Bento PM. Root Canal Treatment and Apical Periodontitis in a Brazilian Population with Type 1 Diabetes Mellitus: A Cross-sectional Paired Study. J Endod. 2020 Jun;46(6):756-762.

19. Saleh W, Xue W, Katz J. Diabetes Mellitus and Periapical Abscess: A Cross-sectional Study. J Endod. 2020 Nov;46(11):1605-1609.
20. Martinho JP et al. Impairment of the angiogenic process may contribute to lower success rate of root canal treatments in diabetes mellitus. Int Endod J. 2021 Oct;54(10):1687-1698.
21. Bender Ib, Seltzer S, Freedland J. The Relationship Of Systemic Diseases To Endodontic Failures And Treatment Procedures. Oral Surg Oral Med Oral Pathol. 1963 Sep;16:1102-15.
22. De Lima AKA, Amorim Dos Santos J, Stefani CM, Almeida de Lima A, Damé-Teixeira N. Diabetes mellitus and poor glycemic control increase the occurrence of coronal and root caries: a systematic review and meta-analysis. Clin Oral Investig. 2020 Nov;24(11):3801-3812.
23. De la Torre-Luna R, Domínguez-Pérez RA, Guillén-Nepita AL, Ayala-Herrera JL, Martínez-Martínez RE, Romero-Ayala ME, Pérez-Serrano RM, Vázquez-Garcidueñas MS. Prevalence of Candida albicans in primary endodontic infections associated with a higher frequency of apical periodontitis in type two diabetes mellitus patients. Eur J Clin Microbiol Infect Dis. 2020 Jan;39(1):131-138.
24. Segura-Egea JJ, Martín-González J, Castellanos-Cosano L. Endodontic medicine: connections between apical periodontitis and systemic diseases. Int Endod J. 2015 Oct;48(10):933-51.
25. Montoya-Carralero JM, Saura-Pérez M, Canteras-Jordana M, Morata-Murcia IM. Reduction of HbA1c levels following nonsurgical treatment of periodontal disease in type 2 diabetics. Med Oral Patol Oral Cir Bucal. 2010 Sep 1;15(5):e808-12.
26. Zayzafoon M, Stell C, Irwin R, McCabe LR. Extracellular glucose influences osteoblast differentiation and c-Jun expression. J Cell Biochem. 2000 Aug 2;79(2):301-10.
27. Su Y, Ye L. Can vitamin D intake assist in improving the outcome of endodontic treatment for diabetic patients? Med Hypotheses. 2010 Apr;74(4):673-5.