UDC: 616.314.17-008.1:616.379-008.64
Review article

PERIAPICAL INFLAMMATORY LESIONS AND DIABETES MELLITUS TYPE II– A REVIEW

Afërdita SALIHU FAZLIU[1*], Marina KACARSKA[2], Uran HALIMI[3], Blerina KOLGECI[4], Gazmend FAZLIU[5]

[1] *Department of Oral Surgery, AAB College, Prishtina, Republic of Kosovo*
[2] *Department of Oral Surgery, Dental Faculty, Ss. Cyril and Methodius University, Skopje, Republic of Macedonia*
[3] *Department of Oral Surgery, Dental School, University of Prishtina "Hasan Prishtina", Prishtina, Republic of Kosovo*
[4] *Department of dental hygiene UNI Universum international College, Prishtina, Republic of Kosovo*
[5] *Dental Clinic Vlera Dent Prishtina, Republic of Kosovo*

Abstract

Periapical periodontitis is a chronic inflammatory disease, caused by endodontic infection, and its development is regulated by the host immune/inflammatory response. Metabolic disorders, which are largely dependent on life style such as eating habits, have been interpreted as a "metabolically-triggered" low-grade systemic inflammation and may interact with periapical periodontitis by triggering immune modulation. Diabetes mellitus (DM) is a group of complex multisystem metabolic disorders due to a deficiency in insulin secretion caused by pancreatic β-cell dysfunction and/or insulin resistance in liver and muscle.
Objective: In this paper, the current status of knowledge regarding the relationship between periapical inflammation and diabetes mellitus type II is reviewed.
Material and method: Research was conducted on scientific papers published on Medline - Pub med in the past 10 years (from 2012-2022). The search was performed using the Mesh (Medical Subject Headings) key words: periapical inflammatory lesions, periapical periodontitis and diabetes mellitus type II.
Results: Several studies have analyzed the possible association between periapical inflammatory lesions and diabetes mellitus type II. The results of studies carried mainly in animal models, less in humans suggested association between endodontic variables such as apical periodontitis, root canal treatment and diabetes mellitus type 2.The demonstration of association does not prove by itself the existence of a cause-effect relationship.
Conclusion: A review of the literature showed connection between periapical inflammatory lesions and diabetes mellitus type II, but prospective case control clinical studies are needed for further clarifying this relation.

Keywords: periapical inflammatory lesions, periapical periodontitis, diabetes mellitus type II.

1. Introduction

Periapical inflammatory lesions are most frequent inflammatory disease in jaw bones.
The prevalence of apical periodontitis (AP) in Europe has been reported to affect 61% of individuals and 14% of teeth, and increase with age. Likewise, the prevalence of root canal treatment (RCT) in Europe is estimated to be around 30-50% of individuals and 2-9% of teeth with radiographic evidence of chronic persistent AP in 30-65% of root filled teeth (RFT) [1].
AP is not only a local phenomenon and for some time the medical and dental scientific community are interested in understanding the possible connection between apical periodontitis and systemic health. Among various systemic diseases, diabetes mellitus stands out as most frequent metabolic disorder that has a dramatic overall impact with high morbidity and mortality.
Type 1 diabetes results from cellular-mediated autoimmune destruction of pancreatic β-cells, which usually leads to total loss of insulin secretion; in contrast, type 2 diabetes is caused by resistance to insulin combined with a failure to produce enough additional insulin to compensate for the resistance. The latter is commonly linked to obesity, which contributes to

https://doi.org/10.62792/ut.amb.v9.i17-18.p2546

insulin resistance through elevation of circulating levels of free fatty acids derived from the adipocytes; these free fatty acids inhibit glucose uptake, glycogen synthesis and glycolysis.
Periapical inflammatory lesions affect the tissues of the periodontal complex and come from a bacterial infection of the canal pulp. These lesions are not just local processes. Thus, periapically released inflammatory cytokines, such as IL-1β, IL-6, IL-8, and TNF-α, may enter the systemic circulation and cause or maintain a state of increased chronic systemic inflammation.
Amongst the environmental factors involved in the pathogenesis of type 2 diabetes, low-grade inflammation seems to occupy a prominent place [2].
This occurs when inflammatory stimuli of infectious origin, such as periodontal disease or apical periodontitis, both oral infections caused by Gram-negative bacteria, activate the innate immune system, causing a high level of pro-inflammatory interleukins [3].
Apical periodontitis could initiate or propagate insulin resistance by enhancing activation of the overall systemic immune response initiated by cytokines. [4]
Through this mechanism, apical periodontitis can induce or perpetuate an elevated chronic systemic inflammatory status, contributing to increased insulin resistance and poor glycemic control [5–6].
However, there is no sufficient scientific evidence supporting a causal effect of periapical inflammation on diabetes control.
Diabetes, on the other hand, is characterized by an increase in chronic systemic inflammation and angiopathy, leading to an increase in susceptibility to infection and poor wound healing. These changes can negatively affect the remission of periapical lesions and reduce the success of endodontic treatment. Exactly high concentrations of circulating cytokines, particularly CRP and interleukin-6 (IL-6), are associated with type 2 diabetes.

2. Aim

In this paper, the status of knowledge regarding the relationship between periapical chronic inflammatory lesions and diabetes mellitus type II is reviewed.

3. Material and methods

In order to achieve the set task, focused research was conducted on scientific papers publishedon Medline - Pub med in the past 10 years (from 2012-2022). The search was performed using the Mesh (Medical Subject Headings) key words: periapical periodontitis, diabetes mellitus, apical periodontitis.
The following criteria were included: the papers should be published as abstracts or full text articles, they should be prospective and retrospective clinical studies, and as most valuable systemic reviews and meta analysis.

4. Results

Studies clarifying the connection between periapical processes and diabetes mellitus in particular are lacking.
The studies that have been done have found a connection between general diseases and periapical changes, some have investigated the periapical changes of endodontically treated teeth in regard to diabetes mellitus type 2, or the healing of periapical lesions after endodontic treatment in people with diabetes and other general diseases.
The effect of high sugar intake on the development of periradicular lesions was investigated by Iwama et al. [7] In this animal study they evaluated the effects of type 2 diabetes on the

development of periradicular lesions. The pulp in the left mandibular first molar was exposed through the occlusal surface in Goto-Kakizaki (GK) rats with spontaneous non-insulin-dependent diabetes mellitus, and in control Wistar rats. Four weeks after pulp exposure, histologic analysis showed that alveolar bone resorption was most severe and the periradicular lesions were largest in diabetic rats given a sucrose solution, suggesting that the metabolic conditions produced by type 2 diabetes enhance the development of periradicular lesions in rats.

In a retrospective cohort study, Segura-Egea et al. [8] investigated the prevalence of AP in patients with and without type 2 diabetes mellitus. This epidemiological study, determined radiographically the prevalence of AP in patients with and without type 2 diabetes mellitus. Results showed that apical periodontitis in at least one tooth was found in 81.3% of diabetic patients and in 58% of control subjects. Amongst diabetic patients 7% of the teeth had AP, whereas in the control subjects 4% of teeth were affected.

In the two consecutive studies Segura-Egea et al [5,9]focused on investigating the connections between apical periodontitis and different systemic diseases, including diabetes mellitus type II. Studies carried out both in animal models and humans suggest an association between endodontic variables, such as apical periodontitis (AP) and root canal treatment (RCT), and diabetes mellitus (DM), tobacco smoking, coronary heart disease and other systemic diseases. They reported a higher prevalence of periapical lesions, delayed periapical repair, greater size of osteolytic lesions, greater likelihood of asymptomatic infections and poorer prognosis for RFT in diabetic patients.

The biological mechanisms by which diabetes mellitus can influence the healing of periapical tissues, affecting the outcome of RCT, are mainly three: impaired innate immunity, hyperglycemia and the formation of irreversibly glycated-proteins forming advanced glycation end products (AGEs). [9]

Bender et al.[10] studied the relationship between systemic diseases, endodontic failures and other treatment procedures. In cases of poorly controlled DM, periapical radiolucency tends to develop during treatment, but if DM is under therapeutic control, periapical lesions heal as readily as in non-diabetics.

As a conclusion they pointed out that inflammatory periapical reactions are greater in diabetic states, and that increased local inflammation causes an intensification of diabetes with a rise in blood glucose, placing the patient in an uncontrolled diabetic state. This often requires an increase in insulin dosage or therapeutic adjustment. Removal of the inflammatory state usually creates a need for a lesser amount of insulin for diabetic control.

5. Discussion

Several studies investigated the connection between diabetes mellitus type II and periapical processes, including also the changes that occur around the root of endodontically treated teeth or the consequences that may occur.

In a cross-sectional study López-López et al [11] examined radiographic records of 50 adult patients with a history of well-controlled type 2 diabetes mellitus (DM) (study group) and 50 age and sex matched subjects with no history of DM (control group). Periapical status of all teeth was assessed radiographically using the Periapical Index Score (Orstavik, 1986).

Result of the study found higher prevalence of apical periodontitis in patients with diabetes mellitus as well as higher number of root canal treatment RCT.

Marotta P.S [12] investigated the prevalence of AP in diabetic patients compared with matched nondiabetic patients and the effect of glycemic control on the incidence of AP. In this cross-sectional study carried out in adult Brazilian population using full mouth radiographs and Strindberg's criteria for the diagnostic of AP, found that AP was significantly

more common in teeth from diabetic individuals (15%) than in nondiabetic controls (12%).The significance was mostly because of the prevalence of AP in untreated teeth: the frequency of AP lesions in untreated teeth was significantly higher in teeth of type 2 diabetics (10%) compared to control (7%).

The results of studies suggest an association between DM and a higher prevalence of AP, odontogenic infections and greater size of periapical lesions.

The following systematic review and meta-analysis studied available scientific evidence on the association between diabetes and the presence of radiolucent periapical lesions (RPLs) in root-filled teeth (RFT). It was concluded that diabetes is significantly associated to higher prevalence of periapical radiolucency in endodontically treated teeth, being an important putative pre-operative prognostic factor in RCT(root canal treatment).[13]

Uncontrolled or poorly controlled diabetes mellitus may be a risk factor for the development of large and/or debilitating periapical infections.

Fouad et al. [14] induced periapical lesions in first molars of female nonobese diabetic (NOD) mice and measured periapical lesion size histomorphometrically.

The objectives of this investigation were to:(i) determine the effect of diabetes mellitus on the pathogenesis of periapical lesions with or without specific bacterial inoculations at the exposure sites, and (ii) test the sensitivities of two microbiological techniques in detecting the persistence of the bacterial inoculum in exposed pulps of nonobese diabetic (NOD) mice. Periapical lesions were induced in first molars of 29 female NOD mice and 31 controls .Then, they measured periapical lesion size histomorphometrically, observing more pronounced periapical lesions in diabetic rates compared with controls.

Bain et al. [15] described the development of insulin resistance in pregnant rats with induced periapical abscesses. Endodontically affected pregnant rats had increased interleukins and serum TNFa levels, together with significant increases in blood glucose and serum insulin concentrations.

Liu et al. [16] reported that metformin, one of the antihyperglycemic agents commonly used for the treatment of type 2 diabetes, decreases periapical bone loss area after pulp exposure in Wistar rats through lowering the RANKL/osteoprotegerin (OPG) ratio, reducing the number of osteoclasts and bone resorption areas.

Experimental studies support the influence of apical periodontitis on glucose and glycated hemoglobin levels of diabetic animals. Studies carried out using mice as an experimental model, have reported higher glycaemia, and greater periapical inflammatory infiltrate with more bone resorption in diabetic mice with apical periodontitis, compared to control animals [16].

A diabetic state was induced with streptozotocin. Apical periodontitis was induced by dental exposure to the oral environment. Periodontal disease was induced by periodontal ligature. Blood glucose concentrations were measured at 0, 6, 30 and 60 days. After euthanization, rat maxillae were excised and processed for histopathology and for measurement of HbA1c levels by ion exchange chromatography. Data were tabulated and subject to statistical analysis. Additionally, diabetic mice with periapical lesions presented higher levels of glycolyzedhemoglobin Hb1Ac, suggesting that concomitant periapical infections may impair metabolic control of diabetes. Glycolyzedhemoglobin Hb1Ac is an established marker for diabetic control.Glycated hemoglobin (HbA1c) levels test is considered the gold standard for diabetic control. Test measures the average glycaemia of the last 2–3 months, allowing to assess the effectiveness of the treatment that the patient receives.HbA1c <6,5%means well controlled, while HbA1c ≥6,5% ill controlled diabetic condition.

Apical periodontitis significantly increases the levels of inflammatory interleukins in diabetic animals with apical periodontitis. Diabetic animals showed a significant increase of IL-17 levels when compared to control mice [17]. Increased level of IL-17 was also found in

diabetic rats without AP [18], suggesting that diabetes plays an important role in the increment of IL-17.

These findings, together with those of Prieto et al. 2017 [19] who found more aggressive inflammatory infiltrate in the periapical area of diabetic animals, with lower levels of serum albumin and increased level of antioxidant uric acid, support the link between diabetes and periapical inflammation.

In the more recent report Cintra et al [20] investigated the relationship between blood profile and histologic findings in both AP and PD associated with diabetes in Wistar rats.

They concluded that diabetes accelerated the development and progression of AP and PD and caused an increase in average erythrocyte volume as well as leucocyte and neutrophil counts. Both oral infections increase the total number of leucocytes, the number of neutrophils and lymphocytes, and blood glucose concentrations in DM rats.

Britto et al. [21] investigated the prevalence of radiographic periradicular radiolucency in root-filled teeth and untreated teeth in patients with and without diabetes.

The records of 30 subjects with diabetes and 23 control subjects attending the Endodontic Graduate Clinic at the University of Florida, Gainesville, were reviewed. The number of teeth with root canal treatments with and without peri radicular radiolucency and the number of teeth without endodontic treatment but with periradicular lesions were recorded.

Results showed that men with type 2 diabetes who had root canal treatments were more likely to have residual lesions.

Sánchez-Domínguez et al. 2015 [22] also performed a cross-sectional study evaluating the glycated hemoglobin levels of diabetic patients in relation to their periapical status. Thus, 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. Their results revealed that the periapical state was significantly associated with HbA1c levels.

Multivariate logistic regression analysis showed that worse periapical status correlated significantly with HbA1c levels ≥6.5% in patients with type 2 diabetes ($p = 0.03$).

Astolphi et al. [23] found that the presence of a periapical lesion can have detrimental effects on insulin signaling and cause insulin resistance.

The association between the diabetic status and a slower healing of the periapical lesion has been confirmed by systematic reviews with meta-analysis.

Nagendrababu V. et al [24] performed systematic review developed and registered in the PROSPERO database. Four electronic databases (PubMed, EBSCHOhost, Cochrane and Scopus databases) were used to perform a literature search until July 2019. This systematic review concluded that diabetes is a main pre-treatment risk factor for root canal treatment.

The results of studies carried out both in animal models and humans suggest an association between endodontic variables, that is AP and RCT, and diabetes mellitus type 2.The demonstration of association does not prove by itself the existence of a cause-effect relationship. Hence the motive for further clinical investigations.

6. Conclusion

The analysis of the studies included in this review suggests that there is an association between apical lesions and diabetes mellitus, and that there is link between glycemic control as a marker for diabetic control and periapical status. However, the type and quality of the studies carried on humans are insufficient for understanding the true nature of this relation. Further prospective, case control studies are needed for clarifying these relation.

References

[1] J.Segura-Egea 1 , J Martín-González 1 , L Castellanos-Cosano 2 . Endodontic medicine: connections between apical periodontitis and systemic diseases Int Endod J. 2015Oct;48(10):933-51.

[2] Tunes, R.S.; Foss-Freitas, M.C.; Da Rocha Nogueira-Filho, G. Impact of periodontitis on the diabetes-related inflammatory status. J. Can. Dent. Assoc. 2010, 76, a35.]

[3] Montoya-Carralero, J.M.; Saura-Pérez, M.; Canteras-Jordana, M.; Morata-Murcia, I.M. Reduction of HbA1c levels following nonsurgical treatment of periodontal disease in type 2 diabetics. Med. Oral Pat

[4] A.Ashwatha Pratha , Dr.S.Jayalakshmi Saveetha Dental College,ChennaiRelationship between Diabetes Mellitus and Pulpal Infection & Periapical Diseases

[5] Segura-Egea, J.-J.; Castellanos-Cosano, L.; Machuca, G.; López-López, J.; Martín-González, J.; Velasco-Ortega, E.; Sánchez-Domínguez, B.; López-Frías, F.J. Diabetes mellitus, periapical inflammation and endodontic treatment outcome. Med. Oral Patol. Oral Cir. Bucal. 2012, 17, e356–e361. [CrossRef]

[6] Verhulst, M.J.L.; Loos, B.G.; Gerdes, V.E.A.; Teeuw, W.J. Evaluating All Potential Oral Complications of Diabetes Mellitus. Front. Endocrinol. (Lausanne) 2019, 10, 56ol

[7] Iwama A, Nishigaki N, Nakamura K, Imaizumi I, Shibata N, Yamasaki M. The effect of high sugar intake on the development of periradicular lesions in rats with type 2 diabetes. J Dent Res. 2003;82:322–325. [PubMed] [Google Scholar] . Oral Cir. Bucal 2010, 15, e808–e812.

[8] Segura-Egea JJ, Jiménez-Pinzón A, Ríos-Santos JV, Velasco-Ortega E, Cisneros-Cabello R, Poyato-Ferrera M. High prevalence of apical periodontitis amongst type 2 diabetic patients. Int Endod J. 2005;38:564–569.

[9] Segura-Egea, J.J.; Martín-González, J.; Castellanos-Cosano, L. Endodontic medicine: Connections between apical periodontitis and systemic diseases. Int. Endod. J. 2015, 48, 933–951. [CrossRef]

[10] Bender IB, Seltzer S, Freedland J. The relationship of systemic diseases to endodontic failures and treatment procedures. Oral Surg Oral Med Oral Pathol. 1963;16:1102–1115. [PubMed] [Google Scholar]

[11] López-López J., Jané-Salas E., Estrugo-Devesa A., Velasco-Ortega E., Martín-González J., Segura-Egea J.J. Periapical and endodontic status of type 2 diabetic patients in Catalonia, Spain: A cross-sectional study. J. Endod. 2011;37:598–601. doi: 10.1016/j.joen.2011.01.002. [PubMed] [CrossRef] [Google Scholar]

[12] Marotta P.S., Fontes T.V., Armada L., Lima K.C., Rôças I.N., Siqueira J.F., Jr. Type 2 diabetes mellitus and the prevalence of apical periodontitis and endodontic treatment in an adult brazilian population. J. Endod. 2012;38:297–300.

[13] Segura-Egea J.J., Martín-González J., Cabanillas-Balsera D., Fouad A.F., 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;20:1133–1141.

[14] Fouad A, Barry J, Russo J, Radolf J, Zhu Q. Periapical lesion progression with controlled microbial inoculation in a type I diabetic mouse model. J Endod. 2002;28:8–116. [PubMed] [Google Scholar]

[15] Bain JL, Lester SR, Henry WD, Naftel JP, Johnson RB (2009) Effects of induced periapical abscesses on rat pregnancy outcomes. Archives of Oral Biology 54, 162–71.

[16] Liu L, Zhang C, Hu Y, Peng B (2012) Protective effect of metformin on periapical lesions in rats by decreasing the ratio of receptor activator of nuclear factor kappa B ligand/osteoprotegerin. Journal of Endodontics 38, 943–7.

[17] Cintra L.T., Samuel R.O., Azuma M.M., Ribeiro C.P., Narciso L.G., de Lima V.M., Sumida D.H., Coclete G.A., Dezan-Júnior E., Gomes-Filho J.E. Apical periodontitis and periodontal disease increase serum IL-17 levels in normoglycemic and diabetic rats. Clin. Oral Investig. 2014;18:2123–2128. doi: 10.1007/s00784-014-1192-7. [PubMed] [CrossRef] [Google Scholar]

[18] Azuma M.M., Gomes-Filho J.E., Prieto A.K., Samuel R.O., de Lima V.M.F., Sumida D.H., Ervolino E., Cintra L.T.A. Diabetes increases interleukin-17 levels in periapical, hepatic, and renal tissues in rats. Arch. Oral Biol. 2017;83:230–235. doi: 10.1016/j.archoralbio.2017.08.001. [PubMed] [CrossRef] [Google Scholar]

[19] Prieto A.K.C., Gomes-Filho J.E., Azuma M.M., Sivieri-Araújo G., Narciso L.G., Souza J.C., Ciarlini P.C., Cintra L.T. Influence of Apical Periodontitis on Stress Oxidative Parameters in Diabetic Rats. J. Endod. 2017;43:1651–1656. doi: 10.1016/j.joen.2017.05.014. [PubMed] [CrossRef] [Google Scholar]

[20] Cintra LT, da Silva Facundo AC, Prieto AK et al. (2014c) Profile and histology in oral infections associated with diabetes. Journal of Endodontics 40, 1139–44.
[21] Britto LR, Katz J, Guelmann M, Heft M. Periradicular radiographic assessment in diabetic and control individuals. Oral Surg Oral Med Oral Pathol Oral RadiolEndod. 2003;96:449–452. [PubMed] [Google Scholar]
[22] Sánchez-Domínguez B., López-López J., Jané-Salas E., Castellanos-Cosano L., Velasco-Ortega E., Segura-Egea J.J. Glycated hemoglobin levels and prevalence of apical periodontitis in type 2 diabetic patients. J. Endod. 2015;41:601–606.
[23] Astolphi RD, Curbete MM, Colombo NH, Shirakashi DJ, Chiba FY, Prieto AK, et al. Periapical lesions decrease insulin signal and cause insulin resistance. J Endod. 2013 M
[24] Nagendrababu V., Segura-Egea J.J., Fouad A.F., Pulikkotil S.J., Dummer P.M.H. Association between diabetes and the outcome of root canal treatment in adults: An umbrella review. Int. Endod. J. 2019