

Why is it necessary to screen for periodontal disease in diabetic patients?

Rucsandra Elena Danciulescu Miulescu^{1,2}, Diana Loreta Paun¹, Loreta Guja¹, Oana Alexandra Mladin¹, Radu Ilinca¹, Iosif Cosmin Trebuian³, Iuliana Gherlan^{1,4}

¹"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

²"N.C.Paulescu" National Institute of Diabetes, Nutrition and Metabolic Diseases, Bucharest, Romania

³"Victor Babes" University of Medicine and Pharmacy, Timisoara, Romania

⁴"C. I. Parhon" National Institute of Endocrinology, Bucharest, Romania

ABSTRACT

Periodontal diseases include gingivitis (inflammation of gingiva caused by the bacterial biofilm) and periodontitis involving loss of the supporting structures around the teeth, respectively cementum, periodontal ligament and alveolar bone. Diabetes increases the risk of periodontal diseases; the plausible mechanisms are: alterations in the immunoinflammatory response of bacteria, increased bone loss, the decrease in matrix-producing cells to maintain the periodontium, microvascular changes and alteration in collagen synthesis and metabolism. Treatment of periodontitis influence glycemic control in diabetic patients and intervention trial suggests that this can generate a reduction of circulating inflammatory markers and improves metabolic control in diabetic patients. International forums recommend oral examination as a component of medical care for diabetic patients. Our review summarizes current information on the association of diabetes with periodontal disease.

Keywords: diabetes, gingivitis, periodontitis

INTRODUCTION

Periodontal diseases include gingivitis (inflammation of gingiva caused by the bacterial biofilm) and periodontitis involving loss of the supporting structures around the teeth, respectively cementum, periodontal ligament and alveolar bone. In 1999 the International Workshop for a Classification of Periodontal Diseases and Conditions proposed a classification of periodontitis which included: chronic periodontitis, aggressive periodontitis, periodontitis as a manifestation of systemic disease, necrotizing periodontitis and periodontal abscesses [1]. Tonetti MS and coworkers proposed in 2018 a new classification of periodontal disease; based on pathophysiology the authors identified three different forms, respectively: necrotizing periodontitis, periodontitis associated with systemic disease and periodontitis [2]. Periodontal disease is generated by an inflammatory host response to the biofilm present around the teeth. In addition to the pathogenic mechanism mentioned above, other risk

factors are involved in the appearance of the condition. The risk factors involved in the appearance of the disease, mentioned in the specialized literature are genetic disorders, systemic diseases (diabetes, haematological, immunosuppressive, neoplastic diseases), and lifestyle (oral hygiene, smoking) [3]. Periodontal disease is considered as the 6th complication of diabetes [4]. In 2009, the International Diabetes Federation (IDF) highlighted the importance of oral health for diabetic patients; the organization has developed a guideline on the management of periodontal disease associated with diabetes mellitus. The recommendations of IDF are: "Enquire annually as to whether each person with diabetes follows local recommendations for day-to-day dental care for the general population, and (where access permits) attends a dental professional regularly for oral health check-ups. Enquire at least annually for symptoms of gum disease (including bleeding when brushing teeth, and gums which are swollen or red). In those people not performing adequate day-to-day dental care, remind

Corresponding author:

Diana Loreta Paun

E-mail: dianaloreta_paun@yahoo.com

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them that this is a normal part of diabetes self-management, and provide general advice as needed. Advise those not attending for regular dental check-ups on the importance of doing so (where access permits). In those people with possible symptoms of gum disease, advise them to seek early attention from a dental health professional. Education of people with diabetes should include an explanation of the implications of diabetes, particularly poorly controlled diabetes, for oral health, especially gum disease” [5]. In 2023 American Diabetes Association (ADA) published Standards of Care in Diabetes. It is mentioned that periodontal disease is more prevalent and more severe in diabetic patients compared to those without this condition. It is recommended the screening and control of the progression of periodontitis [6]. Our review summarizes current information on the association of diabetes with periodontal disease.

DIABETES AND PERIODONTITIS – TWO INTERRELATED DISEASES

Khader YS et al have published in the *Journal of Diabetes and its Complications* a meta-analysis of the periodontal status of diabetic patients compared with nondiabetic subjects. The study includes an analysis of publications from 1970 through 2003 in the MEDLINE database. The results revealed that diabetic patients had poor oral hygiene, a higher severity of gingival and periodontal diseases [7].

Meale BL and Oates TW analyzed over 200 articles published in the last 50 years on the relationship between diabetes and periodontal diseases. The authors note that diabetes increases the risk of periodontal diseases; the plausible mechanisms are: alterations in the immunoinflammatory response of bacteria, increased bone loss, the decrease in matrix-producing cells to maintain the periodontium, microvascular changes, alteration in collagen synthesis and metabolism [8].

The alterations in immunoinflammatory response and increased bone loss. The immune cells, respectively: neutrophils (polymorphonuclear cells), monocytes and macrophages are able to phagocytose and destroy infectious agents [9]. The function of these cells appears to be altered according to studies published in the literature. The cells mentioned above produce more inflammatory mediators and reactive oxygen species that are involved in cell death and alteration of periodontal tissue [10]. The monocyte and macrophage cells may exhibit hyperresponsiveness in response to bacterial antigens leading to increased production of proinflammatory mediators such as interleukin 6 and 1 alpha and tumour necrosis alpha (IL-6, IL-1 α , TNF- α) [11]. Another cytokine involved in inflammatory processes is the receptor activator of nuclear factor kappa ligand (RANKL). TNF- α and RANKL are involved in alveolar bone resorption [12].

The decrease in matrix-producing cells to maintain the periodontium. Diabetic patients are susceptible to the destruction of connective tissue in the gingival and periodontal ligament. The pathogenic pathways include the accumulation of advanced glycation endproducts (AGEs) and augmented expression of receptors for AGEs (RAGE) [13]. AGEs are irreversible products of glycation and oxidation of proteins which accumulate in diabetic tissue and plasma. The relation of AGEs with the deterioration of periodontal status in diabetic patients has been evaluated by Takeda M and coworkers. The authors have evaluated the levels of glycated haemoglobin (HbA1c), AGEs, C-reactive protein and cytokines in 97 type 2 diabetes with and without periodontitis. The results of the study highlighted that “Serum AGEs were significantly associated with deterioration of periodontitis, whereas no other serum biochemical marker showed a clear relationship with that condition” [14]. Studies in animal models have shown that AGEs induce oxidant stress in the gingival which may be involved in accelerated periodontal disease in diabetic patients [15]. In 2000, a study by Lalla E et al. highlighted that the interaction of AGEs with RAGE on cells in diabetic periodontium of mice is associated with excessive inflammation and alveolar bone loss [16].

The mechanisms by which AGEs are involved in the appearance of periodontitis can be represented by:

- increased gingival destruction,
- alteration of the alveolar ligament,
- alveolar bone resorption.

Microvascular changes. The microangiopathic alterations characteristic of diabetes mellitus are also present at the level of periodontal tissue which drives growth susceptibility to infectious at the level of periodontium. Nitta H et al. evaluated the relationship between periodontitis and microvascular complications in a multicenter cross-sectional study, which included 620 patients with type 2 diabetes. The authors concluded that “The number of microvascular complications is a risk factor for more severe periodontitis in patients with type 2 diabetes, whereas poor glycemic control is a risk factor for increased prevalence and severity of periodontitis” [17]. Sadzeviciene R and coworkers evaluated the periodontal disease in 126 diabetic subjects. Of these, severe periodontitis was diagnosed in 27 patients, medium and slight periodontitis in 38, respectively 31 diabetic subjects. Gingivitis was detected in 27 patients. The microvascular complications were associated with the presence of a more severe inflammatory periodontal pathology [18]. The association of periodontal disease with microvascular complications were evaluated in a nationwide cohort study. Have been evaluated 11,353 diabetic patients who received complete oral health. The results of the study revealed that “The presence of periodontitis was associated with an increased risk of

microvascular complications in diabetes patients” [19]. In 2021, Zhang X and collaborators published in the *Journal of Periodontal Research* a meta-analysis that investigated the associated relation between periodontal disease and microangiopathy in patients with type 2 diabetes mellitus. The authors concluded after analyzing 13 cross-sectional studies which included 10,570 patients that “Current evidence has proved that periodontitis is associated with increased risk of diabetic microangiopathy in patients with type 2 diabetes mellitus” [20].

Alteration in collagen synthesis and metabolism. Hyperglycemia can generate impaired production of collagen, results evidenced both *in vitro* [21,22] and *in vivo* studies [23]. The alteration in collagen characteristics in diabetic patients that is the main component of the basement of membranes implicate: impede oxygen diffusion, altered function of polymorphonuclear cells, and diffusion of growth factors. Impaired production of collagen enhanced collagenolytic activity and generated collagen that was more insoluble in diabetic patients [23,24].

IMPACT OF PERIODONTAL DISEASE ON METABOLIC STATUS IN DIABETIC PATIENTS

It has been proven that periodontitis impacting the systemic health and the severity of periodontal disease affects the control of diabetes mellitus [25,26]. It is theorized that passage into systemic circulation of proinflammatory mediators expressed by gingival tissue can generate a poor glycemic control in diabetic patients [27]. Treatment of periodontitis influence glycaemic control in diabetic patients and intervention trial suggest that this can generate reducing of circulating inflammatory markers and HbA1c in diabetic patients. Several meta-analyses have been published on the impact of treatment of periodontal disease of metabolic profile in patients with diabetes mellitus. Teshome A, and Yitayeh A analysed the results of studies published between 2005 and 2015 in four databases. The primary outcome was change of HbA1c after non-surgical periodontal therapy. This systematic review points out a significant reduction of HbA1c on type 2 diabetic patients after periodontal therapy [28]. A systematic review and meta-analysis on randomized controlled trials published in 2021 by Chen YF and coworkers highlighted that periodontal therapy could significantly reduce of HbA1c [29]. Other 2 meta-analyses published in 2016 and 2019 highlighted positive effects of periodontal therapy on metabolic control in patients suffering from type 2 diabetes mellitus [28,30].

Kolte RA and collaborators investigated effect of non-surgical periodontal therapy on metabolic control in 60 patients with type 2 diabetes. The results of the study were published earlier this year in *Contemporary Clinical Dentistry*. The authors found a signifi-

cant decreased in the blood glucose, HbA1c but also improving of systemic inflammatory markers after periodontal therapy [31].

Benefits of non-surgical periodontal therapy in patients with type 2 diabetes and chronic periodontitis were evaluated by El-Makaky Y and Shalaby HK in a randomized controlled trial. Eighty eight subjects with chronic periodontitis and uncontrolled diabetes were enrolled in this trial. The periodontal therapy consists of an oral hygiene and systemic antibiotics respectively amoxicillin 500 mg and metronidazole 400 mg. The results of the trial revealed that non-surgical periodontal therapy improved the metabolic control in diabetic patients with chronic periodontitis [32]. Similar results were reported by Mauri-Obradors E et al. [33], Mizuno H et al. [34], as well as other authors in randomized controlled clinical trial [35-38].

RECOMMENDATIONS ON MANAGEMENT OF PERIODONTAL DISEASE IN PATIENTS WITH DIABETES

In 2020, the Indian Society of Periodontology has published recommendations on management of periodontal disease in patients with diabetes. The authors note that “Patients with a diagnosis of diabetes of any form should undergo a thorough oral examination, including a comprehensive periodontal evaluation, to include a full-mouth pocket chart, and bleeding scores, if indicated by periodontal screening. Patients with diabetes who are diagnosed with gingivitis (early and reversible sign of periodontal disease) should receive oral hygiene instruction, education, and preventive care regimen by the dentist and be monitored regularly for any subsequent periodontal tissue changes. Patients with diabetes presenting with any acute oral/periodontal infections require prompt oral/periodontal care” [39].

The American Diabetes Association recommends promotion of oral health among diabetic patients and oral examination should be a component of medical care for these subjects [6].

CONCLUSION

Diabetes increases the risk of periodontal diseases; the plausible mechanisms are: alterations in immunoinflammatory response of bacteria, increased bone loss, the decrease in matrix-producing cell to maintaining the periodontium, microvascular changes, alteration in collagen synthesis and metabolism. Treatment of periodontitis influence glycaemic control in diabetic patients and intervention trial suggest that this can generate reducing of circulating inflammatory markers and improves metabolic control in diabetic patients. International forums recommend oral examination as a component of medical care for diabetic patients.

REFERENCES

- 1999 International International Workshop for a Classification of Periodontal Diseases and Conditions. Papers. Oak Brook, Illinois, October 30-November 2, 1999. *Ann Periodontol.* 1999 Dec;4(1):i, 1-112. doi: 10.1902/annals.1999.4.1.i.
- Tonetti MS, Greenwell H, Kornman KS. Staging and grading of periodontitis: Framework and proposal of a new classification and case definition. *J Clin Periodontol.* 2018 Jun;45 Suppl 20:S149-S161. doi: 10.1111/jcpe.12945. Erratum in: *J Clin Periodontol.* 2019 Jul;46(7):787. doi: 10.1111/jcpe.13152.
- Verhulst MJL, Loos BG, Gerdes VEA, Teeuw WJ. Evaluating All Potential Oral Complications of Diabetes Mellitus. *Front Endocrinol (Lausanne).* 2019 Feb 18;10:56. doi: 10.3389/fendo.2019.00056.
- Löe H. Periodontal disease. The sixth complication of diabetes mellitus. *Diabetes Care.* 1993 Jan;16(1):329-34. PMID: 8422804.
- IDF Clinical Guidelines Task Force. Guideline on oral health for people with diabetes. Brussels: International Diabetes Federation, 2009.
- ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, et al; on behalf of the American Diabetes Association. 4. Comprehensive Medical Evaluation and Assessment of Comorbidities: Standards of Care in Diabetes-2023. *Diabetes Care.* 2023 Jan 1;46(Suppl 1):S49-S67. doi: 10.2337/dc23-S004. Erratum in: *Diabetes Care.* 2023 Sep 1;46(9):1722. doi: 10.2337/dc23-er09a. Erratum in: *Diabetes Care.* 2023 Sep 01;46(9):1718-1720. doi: 10.2337/dc23-ad09.
- Khader YS, Dauod AS, El-Qaderi SS, Alkafajei A, Batayha WQ. Periodontal status of diabetics compared with nondiabetics: a meta-analysis. *J Diabetes Complications.* 2006 Jan-Feb;20(1):59-68. doi: 10.1016/j.jdiacomp.2005.05.006.
- Mealey BL, Oates TW; American Academy of Periodontology. Diabetes mellitus and periodontal diseases. *J Periodontol.* 2006 Aug;77(8):1289-303. doi: 10.1902/jop.2006.050459.
- Kantari C, Pederzoli-Ribeil M, Witko-Sarsat V. The role of neutrophils and monocytes in innate immunity. *Contrib Microbiol.* 2008;15:118-146. doi: 10.1159/000136335.
- Liu C, Mo L, Niu Y, Li X, Zhou X, Xu X. The Role of Reactive Oxygen Species and Autophagy in Periodontitis and Their Potential Linkage. *Front Physiol.* 2017 Jun 23;8:439. doi: 10.3389/fphys.2017.00439.
- Brownlee M. The pathobiology of diabetic complications: a unifying mechanism. *Diabetes.* 2005 Jun;54(6):1615-25. doi: 10.2337/diabetes.54.6.1615.
- Wada T, Nakashima T, Hiroshi N, Penninger JM. RANKL-RANK signaling in osteoclastogenesis and bone disease. *Trends Mol Med.* 2006 Jan;12(1):17-25. doi: 10.1016/j.molmed.2005.11.007.
- Zizzi A, Tirabassi G, Aspriello SD, Piemontese M, Rubini C, Lucarini G. Gingival advanced glycation end-products in diabetes mellitus-associated chronic periodontitis: an immunohistochemical study. *J Periodontol Res.* 2013 Jun;48(3):293-301. doi: 10.1111/jre.12007.
- Takeda M, Ojima M, Yoshioka H, Inaba H, Kogo M, Shizukuishi S, et al. Relationship of serum advanced glycation end products with deterioration of periodontitis in type 2 diabetes patients. *J Periodontol.* 2006 Jan;77(1):15-20. doi: 10.1902/jop.2006.77.1.15.
- Schmidt AM, Weidman E, Lalla E, Yan SD, Hori O, Cao R, et al. Advanced glycation endproducts (AGEs) induce oxidant stress in the gingiva: a potential mechanism underlying accelerated periodontal disease associated with diabetes. *J Periodontol Res.* 1996 Oct;31(7):508-15. doi: 10.1111/j.1600-0765.1996.tb01417.x.
- Lalla E, Lamster IB, Feit M, Huang L, Spessot A, Qu W, Kislinger T, et al. Blockade of RAGE suppresses periodontitis-associated bone loss in diabetic mice. *J Clin Invest.* 2000 Apr;105(8):1117-24. doi: 10.1172/JCI8942.
- Nitta H, Katagiri S, Nagasawa T, Izumi Y, Ishikawa I, Izumiyama H, et al. The number of microvascular complications is associated with an increased risk for severity of periodontitis in type 2 diabetes patients: Results of a multicenter hospital-based cross-sectional study. *J Diabetes Investig.* 2017;8(5): 677-686. doi: 10.1111/jdi.12633.
- Sadzeviciene R, Paipaliene P, Zekonis G, Zilinskas J. The influence of microvascular complications caused by diabetes mellitus on the inflammatory pathology of periodontal tissues. *Stomatologija.* 2005;7(4):121-4. PMID: 16501314.
- Park MS, Jeon J, Song TJ, Kim J. Association of periodontitis with microvascular complications of diabetes mellitus: A nationwide cohort study. *J Diabetes Complications.* 2022 Feb;36(2):108107. doi: 10.1016/j.jdiacomp.2021.108107.
- Zhang X, Wang M, Wang X, Qu H, Zhang R, Gu J, et al. Relationship between periodontitis and microangiopathy in type 2 diabetes mellitus: a meta-analysis. *J Periodontol Res.* 2021 Dec;56(6):1019-1027. doi: 10.1111/jre.12916.
- Spanheimer RG, Umpierrez GE, Stumpf V. Decreased collagen production in diabetic rats. *Diabetes.* 1988 Apr;37(4):371-6. doi: 10.2337/diab.37.4.371.
- Ramamurthy NS, Golub LM. Diabetes increases collagenase activity in extracts of rat gingiva and skin. *J Periodontol Res.* 1983 Jan;18(1):23-30. doi: 10.1111/j.1600-0765.1983.tb00331.x.
- Balci Yuce H, Karatas Ö, Tulu F, Altan A, Gevrek F. Effect of diabetes on collagen metabolism and hypoxia in human gingival tissue: a stereological, histopathological, and immunohistochemical study. *Biotech Histochem.* 2019 Jan;94(1):65-73. doi: 10.1080/10520295.2018.1508745.
- Ren L, Fu Y, Deng Y, Qi L, Jin L. Advanced glycation end products inhibit the expression of collagens type I and III by human gingival fibroblasts. *J Periodontol.* 2009 Jul;80(7):1166-73. doi: 10.1902/jop.2009.080669.
- Surav AN. Periodontitis and insulin resistance: casual or causal relationship? *Diabetes Metab J.* 2012 Dec;36(6):404-11. doi: 10.4093/dmj.2012.36.6.404.
- Taylor GW, Burt BA, Becker MP, Genco RJ, Shlossman M, Knowler WC, Pettitt DJ. Severe periodontitis and risk for poor glycemic control in patients with non-insulin-dependent diabetes mellitus. *J Periodontol.* 1996 Oct;67(10 Suppl):1085-93. doi: 10.1902/jop.1996.67.10s.1085.
- Barutta F, Bellini S, Durazzo M, Gruden G. Novel Insight into the Mechanisms of the Bidirectional Relationship between Diabetes and Periodontitis. *Biomedicines.* 2022 Jan 16;10(1):178. doi: 10.3390/biomedicines10010178.
- Teshome A, Yitayeh A. The effect of periodontal therapy on glycemic control and fasting plasma glucose level in type 2 diabetic patients: systematic review and meta-analysis. *BMC Oral Health.* 2016 Jul 30;17(1):31. doi: 10.1186/s12903-016-0249-1.
- Chen YF, Zhan Q, Wu CZ, Yuan YH, Chen W, Yu FY, et al. Baseline HbA1c Level Influences the Effect of Periodontal Therapy on Glycemic Control in People with Type 2 Diabetes and Periodontitis: A Systematic Review on Randomized Controlled Trials. *Diabetes Ther.* 2021 May;12(5):1249-1278. doi: 10.1007/s13300-021-01000-6. Epub 2021 Jan 22. Erratum in: *Diabetes Ther.* 2021 May;12(5):1591. doi: 10.1007/s13300-021-01036-8.
- Cao R, Li Q, Wu Q, Yao M, Chen Y, Zhou H. Effect of non-surgical periodontal therapy on glycemic control of type 2 diabetes mellitus: a systematic review and Bayesian network meta-analysis. *BMC Oral Health.* 2019 Aug 6;19(1):176. doi: 10.1186/s12903-019-0829-y.
- Kolte RA, Kolte AP, Bawankar PV, Bajaj VA. Effect of Nonsurgical Periodontal Therapy on Metabolic Control and Systemic Inflammatory Markers in Patients of Type 2 Diabetes Mellitus with Stage III Periodontitis. *Contemp Clin Dent.* 2023 Jan-Mar;14(1):45-51. doi: 10.4103/ccd.ccd_514_21. Epub 2022 Nov 3, 2023.
- El-Makaky Y, Shalaby HK. The effects of non-surgical periodontal therapy on glycemic control in diabetic patients: A randomized controlled trial. *Oral Dis.* 2020 May;26(4):822-829. doi: 10.1111/odi.13256. Epub 2020 Feb 27.
- Mauri-Obradors E, Merlos A, Estrugo-Devesa A, Jané-Salas E, López-López J, Viñas M. Benefits of non-surgical periodontal treatment in patients with type 2 diabetes mellitus and chronic periodontitis: A randomized controlled trial. *J Clin Periodontol.* 2018 Mar;45(3):345-353. doi: 10.1111/jcpe.12858. Epub 2018 Jan 19.
- Mizuno H, Ekuni D, Maruyama T, Kataoka K, Yoneda T, Fukuhara D, et al. The effects of non-surgical periodontal treatment on glycemic control, oxidative stress balance and quality of life in patients with type 2 diabetes: A randomized clinical trial. *PLoS One.* 2017 Nov 16;12(11):e0188171. doi: 10.1371/journal.pone.0188171.

35. Moeintaghavi A, Arab HR, Bozorgnia Y, Kianoush K, Alizadeh M. Non-surgical periodontal therapy affects metabolic control in diabetics: a randomized controlled clinical trial. *Aust Dent J*. 2012 Mar;57(1):31-7. doi: 10.1111/j.1834-7819.2011.01652.x.
36. Raman RP, Taiyeb-Ali TB, Chan SP, Chinna K, Vaithilingam RD. Effect of nonsurgical periodontal therapy verses oral hygiene instructions on type 2 diabetes subjects with chronic periodontitis: a randomised clinical trial. *BMC Oral Health*. 2014 Jun 25;14:79. doi: 10.1186/1472-6831-14-79.
37. Singh S, Kumar V, Kumar S, Subbappa A. The effect of periodontal therapy on the improvement of glycemic control in patients with type 2 diabetes mellitus: A randomized controlled clinical trial. *Int J Diabetes Dev Ctries*. 2008 Apr;28(2):38-44. doi: 10.4103/0973-3930.43097.
38. Telgi RL, Tandon V, Tangade PS, Tirth A, Kumar S, Yadav V. Efficacy of nonsurgical periodontal therapy on glycaemic control in type II diabetic patients: a randomized controlled clinical trial. *J Periodontal Implant Sci*. 2013 Aug;43(4):177-82. doi: 10.5051/jpis.2013.43.4.177.
39. Jain A, Chawla M, Kumar A, Chawla R, Grover V, Ghosh S, et al. Management of periodontal disease in patients with diabetes- good clinical practice guidelines: A joint statement by Indian Society of Periodontology and Research Society for the Study of Diabetes in India. *J Indian Soc Periodontol*. 2020 Nov-Dec;24(6):498-524. doi: 10.4103/jisp.jisp_688_20.

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