Original Article

PERIODONTAL PARAMETERS AND PERIODONTITIS SEVERITY IN TYPE 2 DIABETES PATIENTS WITH CHRONIC COMPLICATIONS

Gizem Torumtay Cin[1], Semin Melahat Fenkci[2], Umut Yiğit[3], Aysan Lektemur Alpan[1]*

[1]*Department of Periodontology, Faculty of Dentistry, Pamukkale University, Denizli, Turkey. Email: gyaprak_dt@hotmail.com*
[2]*Department of Internal Medicine, Faculty of Medicine, Pamukkale University, Denizli, Turkey.*
[3]*Department of Periodontology, Faculty of Dentistry, Uşak University, Uşak, Turkey.*

https://doi.org/10.51847/SysnVQdjrg

ABSTRACT

Long-term hyperglycemia is related to micro and/or macrovascular complications in diabetes mellitus. The interrelationship between diabetes and periodontitis is bi-directional and inflammation is the common feature of both diseases. This study aimed to search the effects of the number of chronic vascular complications in type 2 diabetics on the amount of periodontal tissue destruction and the periodontal disease severity. This cross-sectional study included 127 individuals with type 2 diabetes who developed at least one diabetes-related chronic complication. The severity of periodontitis and the amount of gingival inflammation and periodontal tissue destruction between patients with several vascular complications were compared. We also compared the periodontal parameters and the severity of periodontitis according to glycemic control levels and in terms of the presence of macrovascular complications. All periodontal clinical parameters and periodontal disease severity were significantly higher in patients with 3 and 4 diabetic vascular complications than in patients with fewer complications. In patients without macrovascular complications, the severity of periodontitis was significantly lower compared to those with macrovascular complications (p<0.05). Worsened gingival inflammation was shown in patients with poor glycemic control, but there was no statistically significant difference in PD and CAL. Our findings showed that the severity of periodontal disease was higher as the number of diabetes-related chronic complications increased. The extent of gingival inflammation was elevated with poor glycemic control whereas the amount of periodontal tissue destruction did not change.

Key words: Type 2 diabetes, Periodontitis, Diabetic complications, Inflammation

Introduction

Diabetes is characterized by hyperglycemia due to defects in the mechanisms of insulin metabolism [1-3]. The presence of chronic hyperglycemia, dyslipidemia, and oxidative stress in diabetes can induce long-term dysfunction and damage in various organs [4]. In the long term, poor glycemic control causes microvascular complications such as diabetic retinopathy, neuropathy, and nephropathy, as well as macrovascular complications (peripheral and coronary artery disease, cardiomyopathy, arrhythmia, and cerebrovascular disease) in type 2 diabetic patients. Cardiovascular diseases are the primary reason for mortality in patients with diabetes mellitus. It has been reported that type 2 diabetes causes macrovascular complications through pathogenic pathways such as hyperglycemia and insulin resistance [5]. Endothelial dysfunction and atherosclerogenesis are associated with slowly progressive chronic inflammation for the development of diabetes. The occurrence of diabetic complications is characterized by chronic inflammation. The increase of circulating inflammatory markers in diabetic patients has been shown in clinical studies. The presence of these markers in the blood predicts the development and progression of diabetic complications [6].

Periodontitis is a chronic, infectious disease characterized by the inflammatory destruction of supporting periodontal tissues, which is primarily caused by bacteria and their products in dental plaque [7]. It has been proven that diabetes is directly related to periodontitis. Inflammation is a common property of both diseases and the inflammatory process in periodontal tissues is increased in diabetic patients [8]. Studies report that the prevalence of periodontal disease is 2-3 times higher in people with diabetes mellitus [9]. Periodontal disease severity is especially higher in long-term diabetics with poor metabolic control [10]. Periodontitis is recognized as the 6th complication of diabetes currently [11]. As well as the adverse effects of diabetes on periodontal health that have been indicated, a periodontal disease also hurts glycemic control in diabetic patients. An increase in the host inflammatory response due to the induction of proinflammatory cytokines released into the circulation worsens glycemic control in diabetic patients with periodontitis [12]. Current evidence supports that periodontal infections could increase the risk of diabetic complications [13]. Studies have demonstrated that the prevalence and severity of diabetes complications in extra-oral tissues, such as diabetic neuropathy [14], nephropathy

[15], retinopathy [16], and cardiovascular complications [17] are associated with the severity of periodontitis. However, few studies assess the link between all microvascular complications and periodontal status [18]. The aim of our study is to investigate the severity of periodontal disease in individuals with long-term diabetes who have developed one or more vascular complications related to diabetes.

Materials and Methods

The study protocol was approved with protocol number 60116787-020/62180 by the Ethics Committee of Pamukkale University and carried out in accordance with the Declaration of Helsinki. A total of 127 individuals diagnosed with type 2 diabetes for more than 5 years and developing diabetes-related chronic complications were recruited from those patients attending the outpatient clinic at the Department of Endocrinology at Pamukkale University Hospital. Demographic data of the patients, such as age, gender, body mass index (BMI), waist circumference, smoking status, and duration of diabetes, were recorded in the detailed anamnesis form. Patients were classified according to their waist circumference as overweight or obese. Individuals with diabetes diagnosed within the last 5 years and edentate patients were excluded from the study. Participants were also excluded if they were pregnant or breastfeeding, had past periodontal treatment, or reported use of drugs that may affect the periodontal status. Written informed consent was obtained for each participant.

Diagnosis of diabetic microvascular and macrovascular complications

While the presence of atherosclerotic cardiovascular, cerebrovascular, and peripheral arterial diseases was evaluated as macrovascular complications, retinopathy, nephropathy, and neuropathy were considered for microvascular complications. For the diagnosis of retinopathy, microvascular changes in the retina (microaneurysms, bleeding, hard exudates, and newly formed fragile blood vessels) were examined by ophthalmoscopy in dilated pupils. Diabetic nephropathy was diagnosed with the presence of microalbuminuria derived from first morning voids (albumin/creatinine≥30mg/gr). Neuropathy was recorded if the patient had a motor and superficial deep sensation loss and clinical abnormalities of vibration [19]. Atherosclerotic cardiovascular disease history, glycosylated hemoglobin level (HbA1c), total cholesterol (TC), LDL, and HDL cholesterol levels were obtained from the medical records of the patients. Glycemic control was classified into three degrees: good control for HbA1c<7%, fair for HbA1c≥7 to <8%, and poor glycemic control for HbA1c≥8 [20].

Table 1. Demographic characteristics of the study population

Characteristic	mean± std deviation / n	Percent (%)
Age	59.29±11.91	
Gender (female/male)	73/54	57.5/42.5
BMI		
Female	31.85±0.7	
Male	30.15±0.6	
Waist circumstance		
Normal weight	9	7.1
Female overweight/obese	22/49	17.3/38.6
Male overweight/obese	23/24	18.1/18.9
Smoking		
Smoker/non-smoker	16/111	12.6/87.4
Length of diabetes diagnosis		
5-10 years	34	26.8
>10 years	93	73.2
HbA1c (mmol/mol)	8.18±1.64	
Glycemic control		
Good (<7 mmol/mol)	29	22.8
Fair (7-8 mmol/mol)	46	36.2
Poor (≥8 mmol/mol)	52	40.9
Total cholesterol (mg/dl)	185.81±42.79	
HDL cholesterol (mg/dl)	47.94±12.97	
Microvascular complications		
Neuropathy	29	22.8
Retinopathy	22	17.3
Nephropathy	10	7.9

Neuropathy + Retinopathy	25	19.7
Neuropathy + Nephropathy	9	7.1
Retinopathy + Nephropathy	15	11.8
Neuropathy + Retinopathy+ Nephropathy	17	13.4
The number of chronic complications		
1	34	26.8
2	43	33.9
3	37	29.1
4	13	10.2
Macrovascular complication		
(+/-)	73/54	57.5/42.5
Periodontitis severity		
Stage 1	4	3.1
Stage 2	55	43.3
Stage 3	59	46.5
Stage 4	9	7.1

Periodontal assessment

All periodontal and radiographic radiographic measurements of the patients were performed by the same examiner (GTC). The present number of teeth was recorded. Periodontal parameters such as plaque index (PI), gingival index (GI), bleeding on probing (BOP), probing depth (PD), and clinical attachment level (CAL) were measured using the Williams periodontal probe. Probing depth and clinical attachment level were calculated at six surfaces per tooth, whereas plaque index and gingival index were measured at four surfaces per tooth. The severity of periodontitis was determined based on panoramic radiographs and clinical periodontal measurements [21].

Data processing and statistical analyses

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 22. Continuous variables were given as mean and standard deviation and categorical variables as numbers and percentages. The Shapiro-Wilk test was used to test the normality of the data. Statistical significance between groups was analyzed using the Kruskal-Wallis test or Mann-Whitney U-test. Pearson chi-square analysis was used for the differences between categorical variables. Statistical significance was considered as $p \leq 0.05$.

Results and Discussion

127 patients with type 2 diabetes who had at least one of the diabetic microvascular complications were included in this study. The demographic characteristics of the participants are shown in **Table 1**. The length of the diagnosis of diabetes was more than 10 years for approximately 75% of the participants. The rate of patients with poor glycaemic control was 41%. Neuropathy had been diagnosed in twenty-nine subjects (22.8%), twenty-two subjects (17.3%) had retinopathy and ten subjects (7.9%) had nephropathy. At least two microvascular complications were detected in 66 participants (52%).

The percentage of patients with macrovascular diabetic complications was 57.5% of the study population. Sixty-eight (53.6%) subjects had severe periodontitis (stage 3 and stage 4). The number of teeth and the distribution of periodontal parameters according to diabetic complications are summarized in **Table 2**. Significantly fewer teeth were observed as the number of chronic complications related to diabetes increased.

Table 2. Distribution of clinical periodontal parameters according to diabetic complications. a: Kruskal-Wallis test b: Mann Whitney U test. $p < 0.05$ statistical significance * significantly difference compared to 1 complication # significantly difference compared to 2 complications

Characteristic	The number of micro and macrovascular complications				p-value	Macrovascular complication		p-value
	1	2	3	4		+	–	
The number of present teeth	23.3±3.4*	22.6±3.3#	19.7±5.6*#	19±6.3*#	0.008 a	20.9±5.2	22.52±4	0.115 b
PI	1.23±0.3*	1.3±0.3#	1.54±0.3*#	1.53±0.3*#	0.000 a	1.41±0.3	1.32±0.3	0.131 b
GI	1.56±0.3*	1.63±0.2#	1.84±0.2*#	2.06±0.3*#	0.000 a	1.78±0.3	1.63±0.3	0.017 b
PD	2.8±0.3*	2.92±0.4#	3.38±0.5*#	3.69±0.7*#	0.000 a	3.19±0.6	2.98±0.4	0.026 b
CAL	3.07±0.4*	3.15±0.5#	3.74±0.5*#	4.09±0.5*#	0.000 a	3.49±0.6	3.26±0.5	0.034 b
(%) BOP	77.2±14.8*	76.9±11.3#	85.3±15*#	92.8±11.7*#	0.000 a	83.1±14.7	78.3±13.6	0.053 b

While the number of teeth and periodontal parameters were not different between patients with 1 and 2 diabetic complications, PI, GI, PD, CAL, and the percentage of BOP were found to be significantly higher in patients with 3 and 4 diabetic complications compared to individuals with one or two complications (p<0.05), **(Table 2)**. There was no statistically significant difference in periodontal parameters, including the number of teeth, BOP%, and PI, with respect to the presence of macrovascular complications (p>0.05), **(Table 2)**. The percentages of GI, PD, and CAL were significantly higher in subjects with macrovascular complications (p<0.05), **(Table 2)**. The distribution of periodontitis severity according to the number of diabetic complications is shown in **Figure 1**. In patients with 1 and 2 diabetic complications, stage 2 periodontitis was more common, while in those with 3 and 4 complications, stage 3 periodontitis was often detected. Periodontitis severity in the presence of macrovascular complications is shown in **Figure 2**. The severity of periodontitis was greater in patients with macrovascular complications than in those with no macrovascular complications (p<0.05).

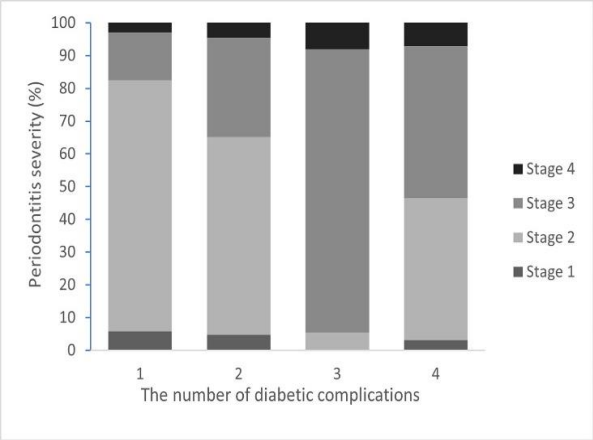

Figure 1. Distribution of periodontitis severity according to the number of diabetic complications

No significant difference was found in the number of teeth compared to glycemic control levels (p>0.05).

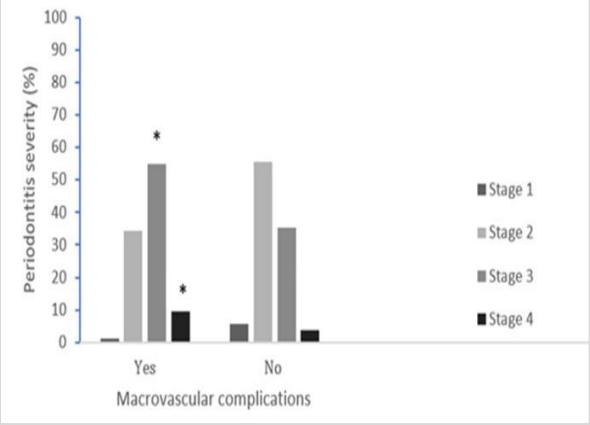

Figure 2. Periodontitis severity according to the presence of macrovascular complications. * p < 0.05 vs patients without macrovascular complications

There was a statistically significant difference between individuals with fair glycemic control and those with poor glycemic control in GI and BOP% (p<0.05). As the glycemic control worsened, higher PD and CAL were observed, but the difference was not statistically significant (p>0.05).

In our study, we aimed to compare the severity of periodontitis and the degree of periodontal inflammation in a population that included individuals with long-term type 2 diabetes who developed several systemic complications. Therefore, both micro and macrovascular complications which determine the chronic inflammatory burden posed by diabetes were evaluated together in type 2 diabetic patients. The severity of periodontal disease was determined clinically and radiographically with full-mouth periodontal measurements. This study addressed the alterations in the periodontium as a result of both micro and macro-angiopathic changes by evaluating periodontal inflammation and alveolar bone loss in type 2 diabetes patients with chronic complications. In our study population, the presence of multiple vascular diabetic complications increased the severity of periodontitis. Also, the presence of macrovascular complications was found to contribute to enhanced periodontal tissue destruction. In diabetes, complications develop as a result of endothelial dysfunction. The damage caused by glucotoxicity and hyperlipidemia progresses with the increase of glycosylated intermediate proteins and the degree of oxidative stress. The increase in micro and macrovascular injury begins in the prediabetic period and macro and micro complications develop in almost 30-50% of the cases when overt diabetes is diagnosed [22]. The duration of diabetes is one of the factors involved in the prevalence of microvascular complications. It has been reported that almost 70% of patients develop retinopathy and approximately 40% develop nephropathy in cases of diabetes exceeding 10 years [23]. The immune response is defective in diabetic patients. There is an impairment in the functions of macrophages, seeding, and opsonization activities at the site of infection. Progressive inflammation in systemic diseases triggers the development of complications. Chronic inflammation induces the activation of the oxidative process, and progressive tissue damage becomes permanent. Long-term hyperglycemia, in particular, is a major contributor to the development of chronic complications [22]. Prolonged exposure of cells to high glucose concentrations, particularly in vascular cells with low glucose transport capacity, leads to intracellular hyperglycemia. Thus, endothelial vascular cells, together with the increase in oxidative stress, become the main target of hyperglycemic damage [24]. Periodontal disease is characterized by an inflammatory host response to bacterial pathogens

accumulating on the surface of the teeth, and its pathogenesis is similar to that of many chronic diseases, such as diabetes [12]. It has been suggested that enhanced proinflammatory mediators in circulation as a result of periodontal diseases may increase the systemic inflammatory loading which is leading to impairment of glycemic control in diabetics and it may cause microvascular diabetic complications as a result [25]. A prolonged hyperglycemic state leads to increased inflammation, oxidative stress, and apoptosis by activating the pathways involved in the formation of advanced glycation end products [26]. This results in an increased risk of complications in individuals affected by both periodontitis and diabetes. It was summarized that there is a link between the severity of periodontitis and diabetic complications [12]. However, there is evidence that indicates that diabetic complications develop more severely in diabetic patients with periodontitis in comparison to periodontally healthy individuals [26]. Even though the relationship between several diabetic complications and periodontitis is multifactorial, the hyperglycemic state seems to be the main mechanism. A 1% reduction in HbA1c level reduces the risk of diabetes-related complications by 25% [27]. In a systemic review that analyzed studies investigating the effects of periodontal disease on glycemic control in diabetic individuals, it was reported that untreated periodontitis leads to worsened glycemic control of diabetic patients over time [28]. The International Diabetes Federation and the European Society of Periodontology workshop report stated that there was a 0.27-0.48% decrease in HbA1c levels of patients with diabetes during 3 months after periodontal treatment [29]. Diabetes increases the risk of the development of deepened periodontal pockets which also indicates a bidirectional relationship between diabetes and periodontal disease [30]. Besides the positive effects of periodontal therapy on glycemic control in diabetics, it has been reported that blood glucose regulation may also be effective in enhancing the healing process of periodontitis [31]. In diabetic individuals with periodontitis, the risk of systemic complications of diabetes may increase because of high HbA1c levels [32]. This risk is 2.5 times higher for macroalbuminuria, 3.5 times higher for end-stage kidney disease, and 3.2 times higher for cardiorenal mortality in individuals with severe periodontitis [33]. Amiri *et al*. found a significant relationship between the severity of periodontitis and diabetic retinopathy [34]. It has been stated that the presence of microvascular complications is a risk factor for severe periodontitis in type 2 diabetes patients, and poor glycemic control affects both the prevalence and severity of periodontitis [18]. While the presence of microvascular diabetic complications increases the risk of periodontitis 2.43 times in type 1 diabetics, this rate has been shown as 2.48 in individuals with coexisting micro and macrovascular diabetic complications [35]. Kocher *et al*. used glycated hemoglobin as a continuous criterion to investigate whether there is a threshold that causes impaired periodontal healing, and they reported that uncontrolled diabetes affects the progression of periodontal disease and tooth loss [36]. In our study, 41% of our participants consist of people with uncontrolled diabetes. We detected an increase in the severity of periodontitis, greater periodontal inflammation, and fewer teeth in type 2 diabetic patients with multiple chronic complications compared to patients with 1 or 2 diabetic complications. The level of glycemic control was found to be associated only with periodontal inflammation.Vascular complications in diabetic patients are present not only in the eyes, kidneys, and nerves but also in other organs such as the heart. The identification and prevention of these complications have an important role in reducing major cardiovascular complications [5]. It has been indicated that periodontal disease may increase the possibility of subclinical atherosclerosis and cardiovascular disease in individuals with diabetes [37]. Periodontal bacteria and their products enhance the systemic inflammatory load by participating in the circulation along with inflammatory molecules and related mediators generated locally in inflamed periodontal tissues. Bacterial persistent inflammatory load on vascular endothelium aggravates atherogenesis and thus increases the risk of cardiovascular disease. In diabetic patients with periodontitis, circulating levels of TNF-α, C-reactive protein, and oxidative stress markers are statistically elevated; however, a significant decrease of these molecules after periodontal treatment has been demonstrated [38]. In a study investigating the relationship between periodontal alterations and cardiovascular parameters in type 2 diabetes patients, CAL was shown to be the most important periodontal parameter in terms of the progression of atherosclerosis [39]. The rate of cardiorenal mortality incidence in diabetic individuals with severe periodontitis is 3.2 times higher than in mild and moderate forms of periodontitis [40]. In our study, we determined that stage 3 and 4 periodontitis were significantly more frequent in cases with macrovascular complications. This result shows that the severity of periodontitis is higher in the atherosclerosis process.In the present study, it was determined that the severity of alveolar bone loss and degrees of periodontal inflammation increased in the presence of both multiple microvascular and macrovascular diabetic complications. Our findings are important to explain that the severity of the alveolar bone loss is influenced by microangiopathic changes in the periodontium due to long-term diabetes. However, due to its cross-sectional design, there is a limitation that the results of this study cannot be used to clarify the causal association between periodontitis and diabetic micro- and macro-angiopathic changes.

Conclusion

In this study, we observed more severe forms of periodontitis as the number of chronic complications related to diabetes increased. This suggests that periodontitis may be a continuous source of chronic inflammation in diabetic patients with multiple systemic complications. The treatment of periodontitis in these cases may be effective in reducing systemic inflammatory loading and oxidative

stress. Therefore, long-term prospective studies seem necessary to investigate the effects of periodontal therapy on diabetic complications.

Acknowledgments: We would like to thank Hande Senol (Pamukkale University, Faculty of Medicine, Department of Biostatistics) for her support in statistical analyses.

Conflict of interest: None

Financial support: None

Ethics statement: Ethic protocol of this study was approved with protocol number 60116787-020/62180 by the Ethics Committee of Pamukkale University.

References

1. Ashurko I, Esayan A, Magdalyanova M, Tarasenko S. Current concepts of surgical methods to increase mucosal thickness during dental implantation. J Adv Pharm Educ Res. 2021;11(3):37-41.
2. Asgari I, Soltani S, Sadeghi SM. Effects of iron products on decay, tooth microhardness, and dental discoloration: a systematic review. Arch Pharm Pract. 2020;11(1):60-82.
3. El Meligy O, Bahannan S, Hassan M, Eltelety S, Kayal R, Qutob A, et al. Oral Health Status and Habits among 6-13 Years Old Children with Limited Access to Dental Care in South Jeddah. Int J Pharm Res Allied Sci. 2019;8(3):109-18.
4. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2010;33 Suppl 1(Suppl 1):S62-9.
5. Avogaro A, Fadini GP. Microvascular complications in diabetes: A growing concern for cardiologists. Int J Cardiol. 2019;291:29-35.
6. Forbes JM, Cooper ME. Mechanisms of diabetic complications. Physiol Rev. 2013;93(1):137-88.
7. Feres M, Figueiredo LC, Soares GM, Faveri M. Systemic antibiotics in the treatment of periodontitis. Periodontol 2000. 2015;67(1):131-86.
8. Nazir MA. Prevalence of periodontal disease, its association with systemic diseases and prevention. Int J Health Sci (Qassim). 2017;11(2):72-80.
9. Preshaw PM, Bissett SM. Periodontitis and diabetes. Br Dent J. 2019;227(7):577-84.
10. Kim EK, Lee SG, Choi YH, Won KC, Moon JS, Merchant AT, et al. Association between diabetes-related factors and clinical periodontal parameters in type-2 diabetes mellitus. BMC Oral Health. 2013;13:64.
11. Löe H. Periodontal disease. The sixth complication of diabetes mellitus. Diabetes Care. 1993;16(1):329-34.
12. Borgnakke WS, Ylöstalo PV, Taylor GW, Genco RJ. Effect of periodontal disease on diabetes: systematic review of epidemiologic observational evidence. J Clin Periodontol. 2013;40 Suppl 14:S135-52.
13. Taylor GW, Borgnakke WS. Periodontal disease: associations with diabetes, glycemic control and complications. Oral Dis. 2008;(3):191-203.
14. Feldman EL, Callaghan BC, Pop-Busui R, Zochodne DW, Wright DE, Bennett DL, et al. Diabetic neuropathy. Nat Rev Dis Primers. 2019;5(1):41.
15. Selby NM, Taal MW. An updated overview of diabetic nephropathy: Diagnosis, prognosis, treatment goals and latest guidelines. Diabetes Obes Metab. 2020;22 Suppl 1:3-15.
16. Sabanayagam C, Banu R, Chee ML, Lee R, Wang YX, Tan G, et al. Incidence and progression of diabetic retinopathy: a systematic review. Lancet Diabetes Endocrinol. 2019;7(2):140-9.
17. Strain WD, Paldánius PM. Diabetes, cardiovascular disease and the microcirculation. Cardiovasc Diabetol. 2018;17(1):57.
18. 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):677-86.
19. Turkish endocrinology and metabolism society. diagnosis, treatment and follow-up guide of diabetes and its complications. Turkish endocrinology and metabolism society. 2020; 14th edition. Available from: https://file.temd.org.tr/Uploads/publications/guides/documents/diabetes-mellitus_2022.pdf
20. American Diabetes Association. 2. Classification and Diagnosis of Diabetes: *Standards of Medical Care in Diabetes-2020*. Diabetes Care. 2020;43(Suppl 1):S14-31.
21. Papapanou PN, Sanz M, Buduneli N, Dietrich T, Feres M, Fine DH, et al. Periodontitis: Consensus report of workgroup 2 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. J Periodontol. 2018;89 Suppl 1:S173-82.
22. Domingueti CP, Dusse LM, Carvalho Md, de Sousa LP, Gomes KB, Fernandes AP. Diabetes mellitus: The linkage between oxidative stress, inflammation, hypercoagulability and vascular complications. J Diabetes Complications. 2016;30(4):738-45.
23. Low Wang CC, Hess CN, Hiatt WR, Goldfine AB. Clinical Update: Cardiovascular Disease in Diabetes Mellitus: Atherosclerotic Cardiovascular Disease and Heart Failure in Type 2 Diabetes Mellitus - Mechanisms, Management, and Clinical Considerations. Circulation. 2016;133(24):2459-502.
24. Barrett EJ, Liu Z, Khamaisi M, King GL, Klein R, Klein BEK, et al. Diabetic Microvascular Disease: An Endocrine Society Scientific Statement. J Clin Endocrinol Metab. 2017;102(12):4343-410.
25. Cardoso EM, Reis C, Manzanares-Céspedes MC. Chronic periodontitis, inflammatory cytokines, and

interrelationship with other chronic diseases. Postgrad Med. 2018;130(1):98-104.
26. Boillot A, Bouchard P, Moss K, Offenbacher S, Czernichow S. Periodontitis and retinal microcirculation in the Atherosclerosis Risk in Communities study. J Clin Periodontol. 2015;42(4):342-9.
27. Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ. 2000;321(7258):405-12.
28. Graziani F, Gennai S, Solini A, Petrini M. A systematic review and meta-analysis of epidemiologic observational evidence on the effect of periodontitis on diabetes An update of the EFP-AAP review. J Clin Periodontol. 2018;45(2):167-87.
29. Sanz M, Ceriello A, Buysschaert M, Chapple I, Demmer RT, Graziani F, et al. Scientific evidence on the links between periodontal diseases and diabetes: Consensus report and guidelines of the joint workshop on periodontal diseases and diabetes by the International Diabetes Federation and the European Federation of Periodontology. J Clin Periodontol. 2018;45(2):138-49.
30. Genco RJ, Borgnakke WS. Risk factors for periodontal disease. Periodontol 2000. 2013;62(1):59-94.
31. Stöhr J, Barbaresko J, Neuenschwander M, Schlesinger S. Bidirectional association between periodontal disease and diabetes mellitus: a systematic review and meta-analysis of cohort studies. Sci Rep. 2021;11(1):13686.
32. Genco RJ, Graziani F, Hasturk H. Effects of periodontal disease on glycemic control, complications, and incidence of diabetes mellitus. Periodontol 2000. 2020;83(1):59-65.
33. Song SJ, Han K, Lee SS, Park JB. Association between the number of natural teeth and diabetic retinopathy among type 2 diabetes mellitus: The Korea national health and nutrition examination survey. Medicine (Baltimore). 2017;96(47):e8694.
34. Amiri AA, Maboudi A, Bahar A, Farokhfar A, Daneshvar F, Khoshgoeian HR, et al. Relationship between Type 2 Diabetic Retinopathy and Periodontal Disease in Iranian Adults. N Am J Med Sci. 2014;6(3):139-44.
35. Oliveira LS, Lira-Junior R, Figueredo CM, Gomes MB, Fischer RG. Self-Reported Periodontitis and Complications in Type 1 Diabetes Patients: A Brazilian Nationwide Survey. Braz Dent J. 2016;27(5):599-603.
36. Kocher T, Konig J, Borgnakke WS, Pink C, Meisel P. Periodontal complications of hyperglycemia/diabetes mellitus: Epidemiologic complexity and clinical challenge. Periodontol 2000. 2018;78(1):59-97.
37. Southerland JH, Moss K, Taylor GW, Beck JD, Pankow J, Gangula PR, et al. Periodontitis and diabetes associations with measures of atherosclerosis and CHD. Atherosclerosis. 2012;222(1):196-201.
38. Liccardo D, Cannavo A, Spagnuolo G, Ferrara N, Cittadini A, Rengo C, et al. Periodontal Disease: A Risk Factor for Diabetes and Cardiovascular Disease. Int J Mol Sci. 201920;20(6):1414.
39. Napora M, Grabowska E, Gorska R. Prospective Analysis of the Relationship Between the State of Periodontal Tissues and Changes in Selected Cardiovascular Parameters in Patients with Type 2 Diabetes. Adv Clin Exp Med. 2016;25(5):879-86.
40. Saremi A, Nelson RG, Tulloch-Reid M, Hanson RL, Sievers ML, Taylor GW, et al. Periodontal disease and mortality in type 2 diabetes. Diabetes Care. 2005;28(1):27-32.