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Original Article

Investigation of the effects of periodontal treatment on glycaemic control: A cross-sectional clinical experiment

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Abstract

Aim: The aim of this study was to evaluate the effects of periodontal treatment on glycaemic control in patients with type II diabetes mellitus.

Materials and Methods: This study was conducted in 40 patients (19 men and 21 women) with periodontitis. The control group, which included 20 patients who had stage I-II periodontitis but were otherwise healthy, underwent periodontal clinical measurements before and after periodontal treatment. The diabetic group, which included 20 patients with type II diabetes mellitus and stage I-II periodontitis, also underwent periodontal clinical measurements before and after periodontal treatment. The study was conducted in patients between the ages of 18 and 69 years. The plasma blood glucose, C-reactive protein (CRP), and glycated haemoglobin (HbA1c) levels were measured at baseline and 3 months. The probing pocket depth (PPD), plaque index (PI), and gingival index (GI) were measured from four surfaces of the relevant teeth of all the patients who participated in the study to determine the periodontal status. The collected numerical data were statistically analysed.

Results: The fasting plasma glucose, CRP, and HbA1c levels significantly decreased in the diabetic group three months after periodontal treatment ($p<0.001$). There was a statistically significant difference in the change in the PPD, PI, and GI from baseline to 3 months between the two groups ($p < 0.05$).

Conclusion: In our study, periodontal treatment positively contributed to glycaemic control by significantly decreasing fasting plasma glucose, HbA1c, and CRP values in patients with type II diabetes.

Keywords: Periodontal treatment; periodontitis; Type II diabetes mellitus

INTRODUCTION

Periodontal disease is a multifactorial disease whose aetiology involves local factors, environmental factors, genetic predisposition, and medical treatments, and it involves complex pathogenesis with changes in the host response. Gingivitis is the most common type of periodontal disease with clinical and histological changes seen only in the gingiva from the four main components of the periodontium, and the primary aetiological agent is dental plaque (1). Periodontitis is an infectious disease that can result in gingiva fibrils, alveolar bone destruction, and subsequent tooth loss with spreading inflammation from the gingiva to tooth-supporting tissues as a result of the effects of bacteria in microbial dental plaque (2).

Although microbial dental plaque is the main factor in periodontitis, various systemic, metabolic, and environmental factors affecting the host immune response also increase the risk of periodontal disease. The most important systemic disease that increases the risk of periodontitis is diabetes mellitus (DM). DM is a common disease characterized by chronic hyperglycaemia due to insulin deficiency or insufficiency that adversely affects quality of life (3). DM is divided into two types: type I and type II. There is a relationship between periodontitis and type II DM, which is the most common type of diabetes. Type II DM is also known as adult-onset diabetes. It usually occurs due to obesity and a lack of physical activity in individuals over the age of 40. Chronic hyperglycaemia in diabetes causes long-term damage, dysfunction, and insufficiency of organs, such as the eyes, kidneys, nerves, heart, and blood vessels (4,5).

Chronic periodontal infections may increase insulin resistance by affecting serum glucose and lipids; increasing the production of cytokines, such as interleukin-1β (IL-1β), IL-6, and tumour necrosis factor-α (TNF-α); and the amount of acute phase proteins, such as C-reactive protein (CRP). For these reasons, periodontitis may increase the risk of complications related to diabetes (6).

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The level of glycaemic control plays a key role in determining the risk of periodontitis. It is assessed by glycated haemoglobin (HbA1c) in the blood. Those with controlled type II DM have an HbA1c level of 5.5–7%. The HbA1c level demonstrates the fasting plasma glucose in the prior three months, which provides. Oral signs of uncontrolled diabetes include dry mouth, dental caries, recurrent periodontal abscesses, halitosis, candida infections, chronic mouth ulcers, and periodontal diseases, such as periodontitis (3,7). Studies have shown that individuals with diabetes are at a greater risk of gingival inflammation, alveolar bone resorption, and attachment loss than healthy individuals (8).

Chronic diseases, such as periodontitis, increase the levels of cytokines, such as CRP, IL-1β, IL-6, TNF-α, and prostaglandin-E2, in circulating blood. As a result of these events, there may be changes in insulin resistance and glucose control deterioration. With traditional periodontal treatments, better glycaemic control is achieved by reducing the systemic inflammatory load in patients with diabetes. Therefore, periodontal treatment in patients with diabetes and severe periodontitis may improve glycaemic control (9,10).

In patients with diabetes, blood CRP and fasting plasma glucose levels may be affected by periodontal infection and inflammation, which suggests that periodontal treatment positively affects metabolic control by reducing the concentration of blood CRP and fasting plasma glucose (6).

This study aimed to examine the effects of nonsurgical periodontal treatment on glycaemic control in patients with type II diabetes mellitus and stage I-II periodontitis.

MATERIALS and METHODS

Study Groups and Design

This study was a cross-sectional study and was conducted with the approval of the Ethics Board of Adiyaman University Faculty of Medicine (Protocol No: 2020-4-1). Our study included patients admitted to the Faculty of Dentistry Department of Periodontology at Adiyaman University. Our study included 40 patients (19 men and 21 women) who were diagnosed with stage I-II periodontitis who were randomly selected from February 2020 to April 2020 and ranged in age from 18 to 69. A total of 20 of these patients had no systemic disease other than type II DM. An informed voluntary consent form was signed by individuals who agreed to participate in the study. Clinical measurements were performed to determine the periodontal status of individuals. The patients included in the study were selected from patients who did not have any systemic disease except for diabetes; had not received any periodontal treatment in the last six months; had not undergone any major surgery in the last six months; and had no bad habits, such as smoking or alcohol abuse. After undergoing oral examinations and a medical history, the patients diagnosed with type II DM were asked to bring new assay results to their next appointment. The fasting plasma glucose, CRP, and HbA1c levels were recorded according to the results of the assay before periodontal treatment. The patients were advised to obtain new blood tests and bring the results to the relevant physician when they came to their appointment three months after the periodontal treatment.

The participants in our study were divided into two groups. The control group included 20 individuals who had stage I-II periodontitis ('initial and moderate chronic periodontitis' according to the previous periodontal classification)(11) but were otherwise healthy, and the diabetic group included 20 individuals with type II DM and stage I-II periodontitis. The fasting plasma glucose, HbA1c, and CRP values of the patients included in the study were recorded at baseline and three months after periodontal treatment. The periodontal status was determined by considering clinical and radiographic data. Patients were included if they had at least six sites with a probing pocket depth (PPD) ≥ 3 mm, clinical attachment level (CAL) ≥ 1 mm, radiographic bone loss < 33%, and radiographic evidence of stage I-II periodontitis(11). For diagnosis of type II DM, a fasting plasma glucose level ≥ 126 mg/dl and an initial HbA1c level ≥ 6% after a full 8 hours of fasting were required, and the patients must have been previously diagnosed with type II DM by a medical doctor. HbA1c was measured by high-performance liquid chromatography (HPLC).

Periodontal Examination

In our study, periodontal examinations of individuals with diabetes at baseline and after periodontal treatment (supra- and subgingival scaling and root planning) were performed on four surfaces of each tooth and recorded. Clinical measurements, including the plaque index (PI) (12); gingival index (GI) (13); PPD (measured from the gingival margin to the pocket base); and CAL (measured from the cemento-enamel junction to the pocket base), which was the primary outcome measure, were obtained from four sites of the teeth with a manual periodontal probe. In this study, the GI and PI scores ranged from 0–3, and the mean values of the four regions of each tooth were noted. The pocket was measured by an experienced periodontist (AT) using a periodontal probe (Williams probe, Hu-Friedy, Chicago, USA) that measured in millimetres. These periodontal indexes were recorded on forms for all patients participating in the study.

Oral Hygiene Education and Periodontal Treatment

Four weeks before periodontal treatment, all patients were enrolled in a hygiene programme and received oral hygiene instructions at 2–6 appointments as well as professional tooth cleaning according to individual needs. Oral hygiene instructions for home care procedures (toothbrushing technique and interdental cleaning) were provided by an experienced periodontist.

Non-surgical periodontal treatment was provided for all patients. This treatment included oral hygiene instructions and full-mouth SRP. Both groups were treated under local anaesthesia. The treatment consisted of an average of four 45-min sessions over three weeks. The SRP was performed by an experienced periodontist (AT) with a hand instrument (Gracey curettes, Hu-Friedy, Chicago, USA) and an ultrasonic device (Pyon 2, W&H, Germany).

Statistical Analysis

The effect size was 1.01; the α value was set at 0.05; and the power of the study was calculated as 93%. Sample size estimation was performed with G*Power (Franz Faul, Germany) version 3.1. Parametric tests were used to compare continuous variables with a normal distribution. A dependent (paired) t-test was used for intra-group comparisons of the variables, and an independent t-test was used for inter-group comparisons. A chi-square (X^2) test was used to compare categorical variables. The relationship between the PI, GI, and PPD scores and the glucose, HbA1c, and CRP levels was assessed with Pearson's correlation coefficient. Statistical analysis of the data was performed with SPSS 15.0 (SPSS, Chicago, USA). The measurements are expressed as the arithmetic mean±standard deviation. The level of significance for all statistical analyses was p<0.05.

RESULTS

The gender, number of participants, and average age distribution of the groups included in the study are shown in Table 1. A total of 40 patients, including 19 (47.5%) men and 21 (52.5%) women aged 18–69 years (48.37±12.35 years), participated in the study.

Table 1. Demographic characteristics of the patients in the study population

Variables	Number of people (N)	Non-diabetic (N/%)	Diabetic (N/%)	P Value
Total number of people	40	20/50.0	20/50.0	
Gender				
Female	21	9/45.0	12/60.0	0.752
Male	19	11/55.0	8/40.0	
Age (mean±SD)	48.37±12.35	44.95±14.34	51.80±9.08	0.932

Table 2. Comparison of intra-group biochemical parameters and clinical periodontal indexes before and after periodontal treatment

Variables	Non-diabetic (mean±SD)	P Value	Diabetic (mean±SD)	P Value
Glucose (mg/dl)				
Baseline	98.05±9.06	P<0.001*	209.13±92.17	0.003*
3 months	88.01±8.53		147.16±47.97	
HbA1c(%)				
Baseline	5.38±0.38	P<0.001*	8.48±2.42	P<0.001*
3 months	5.15±0.40		7.13±1.84	
CRP(mg/L)				
Baseline	1.12±0.33	P<0.001*	6.49±3.41	0.002*
3 months	0.64±0.36		3.36±1.24	
PI				
Baseline	1.74±0.52	0.013*	1.86±0.62	0.005*
3 months	0.90±0.35		1.04±0.52	
GI				
Baseline	1.14±0.38	P<0.001*	1.41±0.59	P<0.001*
3 months	0.59±0.39		0.83±0.61	
PPD(mm)				
Baseline	2.65±0.67	0.001*	3.05±1.17	P<0.001*
3 months	1.85±0.14		2.60±1.16	

Table 3. Comparison of the biochemical parameters and periodontal parameter changes from baseline to three months for the control group and diabetic group after periodontal treatment

Variables	Non-diabetic (mean±SD)	Diabetic (mean±SD)	P- Value
Glucose (mg/dl) (Baseline-3 months)	10.03±6.65	61.97±72.80	0.005*
HbA1c(%) (Baseline-3 months)	-0.23±0.20	-1.35±1.34	0.002*
CRP(mg/L) (Baseline-3 months)	-0.48±0.26	-3.14±2.76	P<0.001*
PI (Baseline-3 months)	-0.84±0.44	-0.81±0.51	0.862
GI (Baseline-3 months)	-0.55±0.21	-0.57±0.42	0.804
PPD (mm) (Baseline-3 months)	-0.80±0.51	-0.45±0.30	0.015*

The intra-group biochemical parameters and periodontal index values of patients with and without diabetes before and after periodontal treatment are shown in Table 2. In the comparison between the control and diabetic groups, a statistically significant difference (P < 0.05) was found between the biochemical parameters (fasting plasma glucose, HbA1c, and CRP) and the periodontal clinical parameters (PI, GI, and PPD). In the diabetic group, the intra-group comparison showed that all parameters significantly decreased (P ≤ 0.005).

The differences between the biochemical parameters and periodontal indexes of the diabetic and control groups are shown in Table 3. In the comparison between the groups, the difference in the plasma blood glucose, HbA1c, and CRP levels between the diabetic group and the control group was statistically significant (P < 0.05). This difference was found to be more significant in the CRP value (P < 0.001).

The correlation between the biochemical parameters and the periodontal parameters of the diabetic group is shown in Table 4. There was no significant correlation between the periodontal parameters and the biochemical parameters before and after periodontal treatment in the diabetic group (P > 0.05). However, there was a correlation between the CRP level and the GI and PPD scores after periodontal treatment.

Table 4. Correlations between the periodontal parameters and the biochemical parameters at baseline and three months after periodontal treatment in the diabetic group

	PI		GI		PPD	
	Baseline	**3-months**	**Baseline**	**3-months**	**Baseline**	**3-months**
Glucose(mg/dl)						
Baseline	r = -0.334 P= 0.151	r = -0.129 P=0.333	r = -0.129 P=0.589	r = -0.267 P=0.255	r = -0.160 P=0.500	r = -0.209 P=0.376
3-months	r = -0.160 P=0.502	r = -0.284 P=0.225	r = -0.001 P=0.997	r = -0.340 P=0.142	r = -0.270 P=0.250	r = -0.302 P=0.195
HbA1c(%)						
Baseline	r = -0.187 P=0.429	r = -0.184 P=0.438	**r = 0.147** **P=0.537**	r = -0.101 P=0.673	r = -0.232 P=0.325	r = -0.260 P=0.268
3-months	r = -0.338 P=0.144	r = -0.247 P=0.294	r = -0.056 P=0.814	r = -0.180 P=0.448	r = -0.185 P=0.434	r = -0.215 P=0.363
CRP(mg/L)						
Baseline	r = -0.143 P=0.548	r = -0.031 P=0.896	**r = 0.093** **P=0.698**	r = -0.114 P=0.633	r = -0.027 P=0.911	r = -0.082 P=0.732
3-months	r = 0.036 P=0.881	r = -0.006 P=0.981	**r = 0.304** **P=0.192**	**r = 0.081** **P=0.734**	**r = 0.121** **P=0.611**	**r = 0.098** **P=0.682**

DISCUSSION

Recent studies have shown that effective periodontal treatment positively affects glycaemic control in patients with diabetes by decreasing biochemical parameters, such as CRP, HbA1c, and fasting plasma glucose levels (14). In our study, systemic inflammation decreased three months after non-surgical periodontal treatment, with a decrease in the CRP, HbA1c, and fasting plasma glucose values. These results may be strong evidence of a relationship between periodontitis and type II DM complications.

Type II DM changes the way blood vessel walls thicken in periodontal tissues. Specifically, as a result of gingival microangiopathy, tissue nutrition is disrupted, and immune cell migration out of the vein worsens. In addition, the presence of chemotaxis and phagocytosis defects in immune cells weakens the defence system. As a result of changes in oral microflora, a decrease in collagen production and an increase in collagenase activity enhance the destruction of periodontal tissues (15). Emrich et al. (16) reported that periodontal disease development was three times greater in type II DM patients than in healthy individuals.

There is strong evidence of decreased pocket depth and changes in clinical attachment gain when probing within 1–3 months after periodontal treatment. Based on this evidence, we decided that clinical and biological evaluations should be performed three months after periodontal treatment (17).

The results of the present study show that although there was a favourable trend in the effect that periodontal disease treatment has on CRP, glucose, and HbA1c levels, this trend was statistically significant. Despite the fact that periodontal disease treatment was successful, non-surgical periodontal therapy without the use of antibiotics was shown to have a favourable effect on the biochemical parameters in patients with type II DM, as all periodontal parameters significantly improved for the diabetic group from baseline and after three months.

The presence of chronic infections, such as periodontitis, leads to an increase in circulating cytokines and CRP from acute-phase proteins. As a result of these events, low-grade chronic infection disrupts glycaemic control by changing the activity of insulin. In recent epidemiological studies, weakly controlled glycaemic conditions have been linked to the presence of periodontal diseases in patients with diabetes (9). An increase in CRP levels has been seen in individuals with insulin resistance, obesity, and periodontal disease. The level of CRP increases in patients with periodontitis but without periodontal treatment. Studies have shown a significant reduction in CRP levels in patients with diabetes after periodontal treatment at an average -0.50 mg/L (95% confidence interval, -0.08 to -0.93) (18).

Periodontal treatment can reduce oral inflammation, and periodontal diseases cause changes beyond the local periodontal environment by systemically reducing CRP levels.

Many studies have now been conducted to investigate the effects of periodontitis treatment on glycaemic control in people with diabetes. Some of these studies are randomised controlled trials, and a consistent finding is that periodontal treatment is associated with reductions in HbA1c of 0.4% (19).

In a study conducted by Grossi et al. (20) in individuals with diabetes, HbA1c values decreased by 0.6% in traditional periodontal treatment, and Promsudthi et al. (21) reported an increase of 0.11% in HbA1c in the control group and a decrease of 0.19% in the diabetic group after three months of periodontal treatment. Kiran et al. (22), who included 44 patients with type II DM and moderate periodontal disease, showed that periodontal treatment significantly reduced HbA1c levels by 0.86% after three months. A meta-analysis showed a decrease in HbA1c of 0.38% after three months of periodontal treatment (9). Although this type of decrease in HbA1c seems small, it can have important clinical effects. Each 1% reduction in HbA1c is associated with a measurably reduced risk of diabetic complications (23). An HbA1c reduction of more than 1% was achieved in this study. Whence, since periodontal treatment appears to have the similar strength to lower HbA1c as other plasma blood glucose-lowering therapies, it may represent an alternative or adjunctive therapy to improve insulin efficacy and glycaemic control in patients with type II DM and periodontitis.

Koromantzos et al. (24) conducted a study in which patients with type II DM underwent traditional periodontal surgery, and the CRP level in the type II DM group decreased by 0.20% after three months compared to that in the control group. In parallel with the above studies, our study showed a significant decrease in CRP by 3.13 mg/L and HbA1c by 1.35% three months after periodontal treatment. In our study, the CRP and HbA1c levels were slightly higher than those in the literature, which may have occurred because of the small sample size. Our sample size was undoubtedly small and may have been biased. Very bigger, multicentre studies are required to confirm our results.

Following periodontal treatments in patients with and without diabetes, improvements in clinical periodontal parameters (i.e., the PPD, GI, PI) have been reported (25,26). Son et al. (25) performed an inter-group comparison on the 28th day after periodontal treatment in patients with diabetes and periodontitis and reported a significant decrease in the PI, GI, and PPD, and Kiran et al. (22), who conducted a study on patients with type II DM and moderate periodontal disease, showed that periodontal treatment significantly reduced the PI, GI, and PPD after three months. Promsudthi et al. (21) reported a significant decrease in the PI and GI three months after periodontal treatment. In addition, Koromantzos et al. (24) studied patients with type II DM who underwent traditional periodontal surgery, and there was a significant decrease in the GI and PPD after six months compared to the control group with type II DM. In our study, a significant decrease in the PPD was observed in the inter-group comparison between the control and diabetic groups. These results overlap with the data in the literature.

Like other symptoms of inflammation, an increase in the CRP level occurs in periodontal diseases. As a result of the periodontal treatments performed in a previous study, the CRP level decreased as well. Decreases in the CRP level after periodontal treatment contribute to improvement in glycaemic control in patients with diabetes (27). In our study, there was a significant decrease in the CRP level between the diabetic and control groups.

Promsudthi et al. (21) compared a type II DM group and a control group three months after periodontal treatment, and there was a significant decrease in the HbA1c, PI, GI, and PPD values in the type II DM group compared to the control group. Dutarte et al. (28) compared a type II DM group with a nondiabetic group, and there was a significant difference in the HbA1c and PPD but no significant difference in the PI and GI values. In our study, there was a significant decrease in the HbA1c, CRP, and PPD values between the groups three months after periodontal treatment, but there was no statistically significant difference in the PI and GI values. Thus, it can be understood that individuals are inconsistent in their oral hygiene habits within three months.

In this study, we found a positive correlation between the GI and PPD and the CRP value in the diabetic group three months after periodontal treatment. However, it was not a statistically significant correlation.

The maintenance in the CRP and HbA1c values was possibly due to the reduction in the PI, GI, and PPD scores. Considering that the patients had periodontal pockets, the effects of periodontal treatment on glycaemic control were actually a consequence of a decrease in gingival bleeding. The significant finding from this trial is the clinical improvement and significant reductions in the CRP and HbA1c levels in type II DM patients after periodontal treatment. Our cross-sectional study provided evidence that the reduction of periodontal infection and development in periodontal inflammation significantly reduced the CRP and HbA1c levels in the short period, thus maintaining glycaemic control.

LIMITATIONS

As limitations of our study, there were some deficiencies in the supply of biochemical marker antibodies due to the coronavirus disease 2019 (COVID-19) pandemic, and there were no qualified people who could study these antibodies in our province. In addition, due to the restrictions of movement between provinces due to the COVID-19 pandemic, we could not analyse these biochemical markers in the surrounding provinces. In future studies, markers such as serum folic acid and homocysteine may be evaluated in the serum or gingival fluid. In addition to HbA1c and CRP, homocysteine decreases and serum folic acid increases may also be associated with periodontal therapy and improvement in metabolic control.

CONCLUSION

Periodontal treatment was shown to have a positive effect on the metabolic control of diabetes. In our study, periodontal treatment significantly contributed to glycaemic control by significantly reducing fasting plasma glucose, HbA1c, and CRP values in patients with type II DM. We believe that periodontal disease treatment in individuals with diabetes may also play an important role in achieving and maintaining glycaemic control.

Competing interests: The authors declare that they have no competing interest.

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REFERENCES

1. Löe H. Periodontal disease: The sixth complication of diabetes mellitus. Diabetes Care 1993;16:329-34.
2. Genco RJ, Borgnakke WS. Risk factors for periodontal disease. Periodontol 2000, 2013;62:59-94.
3. Santos VR, Lima JA, Miranda TS, et al. Relationship between glycemic subsets and generalized chronic periodontitis in type 2 diabetic Brazilian subjects. Arch Oral Biol 2012;57:293-9.
4. Acipinar S, Hendek MK, Erdemir EO. Periodontitis and Diabetes Mellitus: Directional Relationship. J Med Fac Kirikkale Uni 2017;19:103-13.
5. Manfredi M, McCullough MJ, Vescovi P, et al. Update on diabetes mellitus and related oral diseases. Oral Diseases 2004;10:187-200.
6. Grossi SG, Genco RJ. Periodontal disease and diabetes mellitus: a two-way relationship.Ann Periodontol 1998;3:51-61.
7. Moore PA, Guggenheimer J, Orchard T. Burning mouth and peripheral neuropathy in patients with type 1 diabetes mellitus. J Diabetes and Its Complications 2007;21:397-402.
8. Mealey BL, Ocampo GL. Diabetes mellitus and periodontal disease. Periodontology 2000, 2007;44: 127-53.
9. Corbella S, Francetti L, Taschieri S, et al. Effect of periodontal treatment on glycemic control of patients with diabetes: A systematic review and meta-analysis. J Diabetes Investig 2013;4:502-9.
10. Seinost G, Wimmer G, Skerget M, et al. Periodontal treatment improves endothelial dysfunction in patients with severe periodontitis. Am Heart J 2005; 149:1050-4.
11. Papapanou PN, Sanz M, Buduneli N, 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;89:173-82.
12. Silness P, Löe H. Periodontal disease in pregnancy. Acta Odontol Scand 1964;22:121-35.
13. Loe H & Silness J. Periodontal disease in pregnancy. I. Prevalence and severity. Acta Odontol Scand 1963;21:533-51.
14. D'Aiuto F, Gkranias N, Bhowruth D, et al. Systemic effects of periodontitis treatment in patients with type 2 diabetes: a 12 month, single-centre, investigator-masked, randomised trial. Lancet Diabetes Endocrinol 2018;6:954-65.
15. Firatli E. The relationship between clinical periodontal status and insulin-dependent diabetes mellitus. Results after 5 years. J Periodontol 1997;68:136-40.
16. Emrich LJ, Shlossman M, Genco RJ. Periodontal disease in non-insulin-dependent diabetes mellitus. J Periodontol 1991;62:123-31.
17. Al Habashneh R, Alsalman W, Khader Y. Ozone as an adjunct to conventional nonsurgical therapy in chronic periodontitis: a randomized controlled clinical trial. J Periodontal Res 2015;50:37-43.
18. Cutando A, Montero J, Gómez-de Diego R, et al. Effect of topical application of melatonin on serum levels of C-reactive protein (CRP), interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) in patients with type 1 or type 2 diabetes and periodontal disease. J Clin Exp Dent 2015:7;628.
19. Casanova L, Hughes FJ, Preshaw PM. Diabetes and periodontal disease: a two-way relationship. Br Dent J 2014;217:433-7.
20. Grossi SG, Skrepcinski FB, DeCaro T, et al. Treatment of periodontal disease in diabetics reduces glycated hemoglobin. J Periodontol 1997;68:713-9.
21. Promsudthi A, Pimapansri S, Deerochanawong C, et al. The effect of periodontal therapy on uncontrolled type 2 diabetes mellitus in older subjects. Oral Dis 2005;11:293-8.
22. Kiran M, Arpak N, Unsal E, et al. The effect of improved periodontal health on metabolic control in type 2 diabetes mellitus. J Clin Periodontol 2005;32:266-72.
23. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000;321:405-12.

24. Koromantzos PA, Makrilakis K, Dereka X, et al. Effect of non-surgical periodontal therapy on C-reactive protein, oxidative stress, and matrix metalloproteinase (MMP)-9 and MMP-2 levels in patients with type 2 diabetes: a randomized controlled study. J Periodontol 2012;83:3-10.
25. Son A, Pera C, Ueda P, et al. Clinical effects of supragingival plaque control on uncontrolled type 2 diabetes mellitus subjects with chronic periodontitis. Braz J Oral Sci 2012:11;47-51.
26. Ribeiro Edel P, Bittencourt S, Nociti-Júnior FH, et al. The effect of one session of supragingival plaque control on clinical and biochemical parameters of chronic periodontitis. J Appl Oral Sci 2005;13:275-9.
27. Katagiri S, Nitta H, Nagasawa T, et al. Multi-center intervention study on glycohemoglobin (HbA1c) and serum, high-sensitivity CRP (hs-CRP) after local anti-infectious periodontal treatment in type 2 diabetic patients with periodontal disease. Diabetes research and clinical practice 2009;83:308-15.
28. Duarte PM, Bezerra JP, Miranda TS, et al. Local levels of inflammatory mediators in uncontrolled type 2 diabetic subjects with chronic periodontitis. J Clin Periodontol 2014;41:11-8.