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The Effect of Periodontal Therapy on Serum CRP, IL-6 Levels and Periodontal Parameters in Patients Having Poorly and Well Controlled Type 2 Diabetes with Chronic Periodontitis: a 3-month evaluation *

Kronik Periodontitisi Olan Kötü ve İyi Kontollü Tip 2 Diabet Hastalarında Periodontal Tedavinin Serum CRP ve IL-6 Seviyeleri Üzerine Etkisinin Değerlendirilmesi; 3 aylık bir değerlendirme *

Ahmet DAĞ[1]

Ela Tules FIRAT[1]

Ali Kemal KADİROĞLU[2]

[1] Department of Periodontology, Faculty of Dentistry in Dicle University, Turkey,

[2] Department of Internal Medicine, Medicine Faculty in Dicle University, Turkey

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Corresponding Address /Yazışma Adresi:

Ahmet DAĞ
Department of Periodontology,
Dentistry Faculty,
University of Dicle, 21280
Diyarbakır- TURKEY

Fax: + 90 412 248 81 00;
Tel: +90 412 248 81 01

adag@dicle.edu.tr

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duzcetipdergisi@duzce.edu.tr

ABSTRACT

Aim: To evaluate the effect of nonsurgical periodontal therapy on serum C-reactive protein (CRP), interlökin-6 (IL-6) levels and periodontal parameters in patients with poorly and well controlled type 2 diabetes with chronic periodontitis.

Methods: Forty-five patients were included in the study. Of the 45, 30 had type 2 diabetes mellitus with chronic periodontitis (group 1A; poorly controlled group, n = 15, HbA1c ≥ 7% and group 1B; well controlled group, n = 15, HbA1c < 7%) and 15 were systemically healthy (group 2) with chronic periodontitis. Plaque index, gingival index, probing depth, clinical attachment loss, gingival bleeding index scores, serum CRP and IL-6 concentrations were measured at baseline and 3 months after the nonsurgical periodontal therapy.

Results: After the nonsurgical periodontal therapy all periodontal parameters and CRP and IL-6 levels decreased significantly by the third month compared to baseline values in all groups. No statistically significant difference was determined among the groups between baseline and third-month periodontal parameters, or in CRP or IL-6 levels after nonsurgical periodontal therapy.

Conclusion: Improvement in periodontal health is effective on control of systemic infection via reducing serum concentrations of CRP and IL-6 in patients with poorly and well controlled type 2 diabetes with chronic periodontitis. The effects of nonsurgical periodontal treatment seems to be independent of the degree of diabetic status.

Key Words: CRP; IL-6; periodontal therapy; periodontitis; type 2 diabetes mellitus.

ÖZET

Amaç: Kronik periodontitisi olan kötü ve iyi kontrollü tip 2 diabetik hastalarda cerrahi olmayan periodontal tedavinin serum C-reactif protein (CRP), interlökin-6 (IL-6) ve periodontal parametreler üzerine etkisinin değerlendirilmesidir.

Method: Çalışmaya 45 hasta dahil edildi. 30 hasta kronik periodontitisi olan tip 2 diabet hastası idi.(grup 1A; kötü kontrollü grup, n=15, HbA1c ≥ 7% ve grup 1B; iyi kontrollü grup, n=15, HbA1c < 7%) ve 15 hasta ise kronik periodontitisi olan sistemik olarak sağlıklı hastalar (grup 2) idi. Plak indeksi, gingival indeks, cep derinliği, klinik ataçman kaybı, gingival kanama skorları, serum CRP ve IL-6 konsantrasyonları başlangıçta ve cerrahi olmayan periodontal tedaviden 3 ay sonra ölçüldü.

Bulgular: Bütün gruplarda cerrahi olmayan periodontal tedaviden 3 ay sonra başlangıca göre tüm periodontal parametrelerde, serum CRP ve IL-6 seviyelerinde anlamlı azalma elde edildi. Grupların başlangıç ve 3. ay değerleri karşılaştırıldığında ise periodontal parametreler ile serum CRP ve IL-6 seviyelerinde herhangi bir fark tespit edilmedi.

Sonuç: Kötü ve iyi kontrollü tip 2 diabetik hastalardaki periodontal iyileşme, serum CRP ve IL-6 konsantrasyonlarında azalmaya neden olarak sistemik infeksiyonun kontrol altına alınmasında etkilidir. Cerrahi olmayan periodontal tedavinin etkisinin diabetik durumun derecesinden bağımsız olduğu görülmektedir.

Key Words: CRP; IL-6; periodontal tedavi; periodontitis; tip 2 diabetes mellitus.

INTRODUCTION

Periodontitis is much more than a localized oral infection. Periodontal disease has been reported as the sixth complication of diabetes, along with neuropathy, nephropathy, retinopathy, and micro- and macrovascular diseases (1,2). Many studies have been published describing the bidirectional interrelationship between diabetes and periodontal disease. Moreover, periodontal disease has been suggested to be one such type 2 diabetes-triggering subclinical inflammatory state, with recent data indicating that periodontitis is associated with a moderate systemic inflammatory response. In addition, periodontitis and diabetes have been reported to share a common pathogenesis involving an increased inflammatory response at the local and systemic level (3-6).

The main influences of diabetes on periodontal disease appear to be related to alterations in host immunoinflammatory reactions and tissue homeostasis. The increased response of monocytes and macrophages from diabetic patients may be related to the interaction of elevated levels of advanced glycated end-products (AGE) in the periodontium with AGE receptors on these immune cells. However, chronic gram-negative periodontal infections increase insulin resistance and negatively impact glycemic control (7-9).

In recent years, several studies have been published that implicate subclinical chronic inflammation as an important pathogenetic factor in the development of insulin resistance and type 2 diabetes. This opens new perspectives for diagnosis and treatment of early insulin resistance and incipient glucose intolerance. Surrogate markers for this low-grade chronic inflammation include CRP, IL-6 and TNF-alpha (10).

Type 2 diabetes may involve the innate immune system and result from a chronic, low-level inflammatory process. The triggers of such inflammation are many and potentially include oral infection, which may lead to a cascade of events, including increased cytokine production and activation of acute-phase protein synthesis (11). The Insulin Resistance Atherosclerosis Study (IRAS) investigators concluded that chronic inflammation was a new risk factor for type 2 diabetes (12). Within this context, this research could imply that untreated periodontitis, a well-known chronic inflammatory condition, may increase a person's risk of developing type 2 diabetes.

Currently, no consensus exists among researchers as to whether periodontal therapy has an effect on inflammatory mediators (13). Thus, our aim was to examine the effects of nonsurgical periodontal therapy on serum CRP and IL-6 levels in patients with poorly and well controlled type 2 diabetes and nondiabetic patients.

MATERIALS AND METHODS

Forty-five patients with chronic periodontitis were enrolled. Fifteen had poorly controlled diabetes mellitus (group 1A, HbA1c $\geq$ 7%) and 15 had well controlled DM (group 1B, HbA1c <7%) (14). They were compared with a control group of 15 systemically healthy but have same periodontal status with DM group (group 2). Those with DM were selected from patients admitted to the Department of Endocrinology, Dicle University, Diyarbakır, Turkey. Control patients were selected from patients at the Department of Periodontology, Dentistry Faculty, Dicle University. The research was designed as a prospective, controlled clinical study. All patients were informed of the principle of the therapy to be applied, and written informed consent was obtained. Excluded from the study were patients who had chronic microvascular or macrovascular complications, chronic obstructive pulmonary disease, renal or liver disease, malignancies, collagen tissue disease, a history of infection or trauma in the previous 2 weeks, acute infection (e.g., acute gastritis, acute upper/lower respiratory tract, or urinary tract infections), a tendency for bleeding diathesis, findings of congestive coronary deficiency, known coronary artery disease, or a history of regular medication use (e.g., anti-inflammatories, steroids, immuno-suppressants). Pregnant patients and smokers were also excluded.

Inclusion criteria for all 45 chronic periodontitis were patients who had not received any periodontal therapy within the previous 6 months or antimicrobial therapy within the previous 3 months prior to the baseline examination. Having at least 15 teeth, probing depth of (PD) $\geq$ 5 mm in at least four sites and clinical attachment loss (CAL) of $\geq$ 3 mm in at least four sites was also required. The body mass index (BMI) was calculated by dividing the body weight (in kg) by the square of the height (in m; kg/m2) (15).

Glycated hemoglobin was used as a parameter for the long-term metabolic control of the disease (16). In the study, the patients who had been diagnosed with type 2 DM at least 5 years earlier were included and classified according to HbA1c level (group 1A; poorly controlled group, HbA1c $\geq$7%; group 1B; well controlled group, HbA1c <7%)(14). All patients with DM were treated with oral hypoglycaemic antidiabetic agents.

Panoramic radiography was performed. Plaque Index (PI) (17), gingival Index (GI) (18), pocket depth (PD), gingival bleeding index (GBI) (19), and clinical attachment loss (CAL) (20) were recorded at six sites per tooth (distobuccal, buccal, mesiobuccal, distolingual, lingual, mesiolingual), except the third molars, using a Williams' probe. PD was defined as the distance in millimeters from the coronal to the margin of the free gingiva to the bottom of the periodontal pocket. In all cases, CAL was defined as the distance from the cementoenamel junction to the bottom of the pocket.

Before the first session of scaling, all patients received standard oral hygiene instructions, placement of emergency restorations, and extractions of hopeless teeth. The number of sessions varied depending on the individual treatment needs of each patient. Subsequent standard nonsurgical periodontal therapy comprised scaling and root planing, which were performed by the same investigator using standard periodontal curettes and an ultrasonic device, without time limitation. After the therapy was completed, patients underwent no periodontal intervention for 3 months. In addition, medical therapy for DM,

Table 1. Comparison of Demographic Features and BMI among the Groups

Parameters	Group 1A	Group 1B	Group 2	*p*
Gender M/F	5/10[a]	7/8[b]	8/7[c]	0.442[ab], 0.448[ac], 0.951[bc]
Age (years)	53.13±8.47	52.20 ± 7.67	49.5 ± 7.61	1.000, 0.659, 1.000
Vintage of DM (years)	7.33 ± 2.76	7.13 ± 1.84	-	0.818
BMI (kg/m^2)	27.86±4.53	28.00 ± 5.02	23.80 ± 4.58	1.000, 0.057, 0.069

Group 1A: patients with poorly controlled DM. Group 1B: patients with well controlled DM. Group 2: nondiabetic patients; DM, diabetes mellitus; BMI, body mass index; CRP, C-reactive protein; IL-6, interleukin 6; ab, comparison of the values of poorly and well controlled DM patients; ac, comparison of the values of poorly controlled DM and nondiabetic patients; bc, comparison of the values of well controlled DM and nondiabetic patients; Values are shown as the mean ± SD (standard deviation); $p < 0.05$ was accepted as significant.

Table 2. Comparison of Baseline Parameters among Groups

Parameters	Group 1A	Group 1B	Group 2	*p*
PD (mm)	2.84 ± 0.65[a]	2.67 ± 0.45[b]	2.61 ± 0.38[c]	1.000[ab],0.664[ac],1.000[bc]
PI	2.05 ± 0.68	1.82 ± 0.66	2.34 ± 0.52	0.940, 0.663, 0.087
GI	1.32 ± 0.40	1.04 ± 0.31	1.24 ± 0.40	0.106, 1.000, 0.380
GBI (%)	0.33 ± 0.18	0.28 ± 0.12	0.37 ± 0.18	1.000, 1.000, 0.475
CAL (mm)	4.30 ± 0.97	4.25 ± 0.82	4.31 ± 0.59	1.000, 1.000, 1.000
CRP (mg/L)	3.41± 2.71[a]	1.85 ± 1.16[b]	2.47 ± 1.27[c]	0.078, 0.515, 1.000
IL-6 (pg/mL)	5.17 ±1.61	5.21 ± 1.77	5.97 ± 3.53	1.000, 0.974, 0.952
HbA1c(%)	9.96± 1.45	6.26 ± 0.72	5.26 ± 0.40	<0.001,<0.001,0.021

PD, pocket depth; PI, plaque index; GI, gingival index; GBI, gingival bleeding index; CAL, clinical attachment loss

Table 3. Comparison of Third-Month Parameters among Groups

Parameters	Group 1A	Group 1B	Group 2	*p*
PD (mm)	2.37 ± 0.59	2.30 ± 0.43	2.36 ± 0.68	1.000, 1.000, 1.000
PI	0.30 ± 0.22	0.19 ± 0.05	0.19 ± 0.26	0.381, 0.449, 1.000
GI	0.13 ± 0.10	0.09 ± 0.06	0.07 ± 0.03	0.325, 0.085, 1.000
GBI (%)	0.04 ± 0.02	0.04 ± 0.01	0.03 ± 0.02	1.000, 0.802, 1.000
CAL (mm)	3.04 ± 0.81	3.03 ± 0.79	2.91 ± 0.56	1.000, 1.000, 1.000
CRP (mg/L)	3.03 ± 2.20[a]	1.23 ± 0.55[b]	1.36 ± 0.41[c]	0.002, 0.004, 1.000
IL-6 (pg/mL)	4.04 ± 2.07	3.52 ± 0.83	4.25 ± 2.60	1.000, 0.965, 0.980
HbA1c(%)	9.77±1.15[a]	6.05±0.77[b]	5.24±0.27[c]	<0.001[ab],<0.001[ac],0.028[bc]

Table 4. Comparison of Baseline and Third-Month Parameters in Group 1A after the Periodontal Therapy

Parameters	Initial	After 3 months	*p*
CRP (mg/L)	3.41 ± 2.71	3.03 ± 2.20	0.039
IL-6 (pg/mL)	5.17 ± 1.61	4.04 ± 2.07	0.027
PD (mm)	2.84 ± 0.65	2.37 ± 0.59	0.001
PI	2.05 ± 0.68	0.30 ± 0.22	0.009
GI	1.32 ± 0.40	0.13 ± 0.10	0.001
GBI (%)	0.33 ± 0.18	0.04 ± 0.02	0.001
CAL (mm)	4.30 ± 0.97	3.04 ± 0.81	0.001

Table 5. Comparison of Baseline and Third-Month Parameters in Group 1B after Periodontal Therapy

Parameters	Initial	After 3 months	*p*
CRP (mg/L)	1.85 ±1.16	1.23 ± 0.55	0.013
IL-6 (pg/mL)	5.21 ±1.77	3.52 ± 0.83	0.016
PD (mm)	2.67 ±0.45	2.30 ± 0.43	0.001
PI	1.82 ±0.66	0.19 ± 0.05	0.001
GI	1.04 ±0.31	0.09 ± 0.06	0.001
GBI (%)	1.04 ±0.31	0.04 ± 0.01	0.001
CAL (mm)	4.25 ±0.82	3.03 ± 0.79	0.001

Table 6. Comparison of Baseline and Third-Month Parameters in Group 2 after Periodontal Therapy

Parameters	Initial	After 3 months	*p*
CRP (mg/L)	2.47 ± 1.27	1.36 ± 0.41	0.005
IL-6 (pg/mL)	5.97 ± 3.53	4.25 ± 2.60	0.001
PD (mm)	2.61 ± 0.38	2.36 ± 0.68	0.001
PI	2.34 ± 0.52	0.19 ± 0.26	0.001
GI	1.24 ± 0.40	0.07 ± 0.03	0.001
GBI (%)	0.37 ± 0.18	0.03 ± 0.02	0.001
CAL (mm)	4.31 ± 0.59	2.91 ± 0.56	0.001

including medication, diet, and physical therapy, was unchanged. All periodontal parameters and CRP and IL-6 levels were measured at baseline and 3 months following completion of the periodontal therapy.

Venous blood samples were taken from each patient in the morning following an overnight fast between 08:30 and 11:00 before the periodontal examination. After the venous blood samples were taken, they were analyzed immediately in the central laboratory of the Medical Faculty Hospital. CRP levels were assayed using the nephelometric method (IMMAGE®; Beckman Coulter, Fullerton, CA, USA) (21) The normal range was 0.0-8.0 mg/L. The detection limit for CRP was 1.0 mg/L and a serum CRP concentration >8 mg/L was deemed a high CRP level. IL-6 levels were measured using a chemiluminescence method (Immulite 1000 device; Diagnostic Products Corporation, Los Angeles, CA, USA) (22). Statistical analyses were performed using SPSS (13.0 PC; SPSS Inc., Chicago, IL, USA) software. Dependent variables were analysed by the Wilcoxon signed-ranks test and independent variables by a one-way ANOVA post hoc test and Pearson's correlation test. Values are shown as the mean±SD (standard deviation), and $p<0.05$ was deemed to be statistically significant.

RESULTS

Demographic data and BMIs were determined from medical records (Table 1).Serum levels of CRP, IL-6, HbA1c and periodontal parameters of all groups at baseline are shown in Table 2. No significant difference was observed in gender, age, duration of DM, or BMI. The HbA1c values were significantly higher in groups 1A and 1B compared to the control group.

The third month values of the groups are summarized in Table 3. No statistically significant difference was determined in the periodontal parameters, CRP, or IL-6 levels between the patient and control groups. Differences in the HbA1c levels were seen between groups 1A and 1B and the control group.

A statistically significant decrease was found in CRP and IL-6 levels and periodontal parameters in group 1A after the nonsurgical periodontal therapy. A non-significant decrease was observed in the HbA1c values between the baseline and 3 months after the periodontal therapy (Table 4).

In group 1B, in IL-6 and CRP levels, HbA1c values, and all periodontal parameters a significant decrease was determined after the nonsurgical periodontal therapy (Table 5). In group 2, a significant decrease was observed in CRP and IL-6 levels and periodontal parameters after the nonsurgical periodontal therapy (Table 6). Using Pearson's correlation analysis, a positive correlation was determined between CRP and PI ($r=0.687$, $p=0.005$), CRP and GI ($r=0.521$, $p=0.046$), CRP and GBI ($r=0.646$, $p=0.009$), and IL-6 and GBI ($r=0.518$, $p=0.048$).

DISCUSSION

It is presumed that hyperglycemia induces nonenzymatic glycation of protein-yielding advanced glycation end products (AGE), which are postulated to stimulate interleukin-6 (IL-6) expression, triggering the liver to secrete tissue necrosis factor α (TNF-α) and C-reactive protein (CRP). Although the high prevalence of periodontitis among individuals with diabetes is well known by dental researchers, it is relatively unrecognized in the medical community. The expression of the same proinflammatory mediators implicated in hyperglycemia (i.e., IL-6, TNF-α and CRP) have been reported to be associated with periodontal disease (23,24).

Grossi and Genco described a similar process, reporting that AGE is a causative initiator of atherosclerosis in addition to periodontal pathogens. In this model, they proposed that the combination of these 2 pathways, infection and AGE-mediated cytokine up-regulation, explain the increased tissue destruction seen in diabetic periodontitis. This can be viewed as the AGE-related inflammatory process, and oral infection may share a common pathway via TNF-α, and CRP. Several recent studies have reported a strong inflammatory response in periodontitis characterized by increased secretion of inflammatory mediators, primarily proinflammatory cytokines, which can have both local (periodontal destruction) and systemic (impaired glycemic control) effects (25,26).

Therefore we wonder if the nonsurgical periodontal therapy has a beneficial effect on the serum inflammatuar markers in the well and poorly controlled patients. We determined that the response of both groups with DM to periodontal therapy was the same as in the control group.Rodrigues et al. (27) found no difference between baseline periodontal parameters and those at 3 months after periodontal therapy patients having type 2 DM with periodontitis. Grossi et al. (28) also reported a significant decrease in gingival and plaque scores and pocket depth before and in the third and sixth months after periodontal therapy, but no difference was observed between the groups.But two of this study didnot include systemically healty patients to their study.

Tervonen and Karjalainen (29) also reported that they found no statistical difference in terms of periodontal health between the diabetic and control groups, but that they observed a rapid increase in subgingival calculus formation in sites with PD ≥4 mm and recurrence in pocket differences in the poorly controlled group. They emphasized that such patients should be enrolled in a maintenance periodontal therapy program. In agreement with our data Wesfelt et al. (30) and Christgau et al. (20) also found no correlation between HbA1c and periodontal healing response.

Pickup et al. (31) suggested that plasma IL-6 concentrations were significantly higher in patients with DM than in nondiabetics. However, Pickup et al. only enrolled patients with poorly controlled DM in their study and we can not learn anything about the periodontal status of those patients. Pradhan et al. (32) reported that CRP and IL-6 levels were significantly higher in those with DM than in the control group, and that they may play a role in inflammation in diabetogenesis.

Some authors have reported that healthy patients with periodontitis have elevated circulating CRP levels (33-39). D'Aiuto et al. (40) stated that CRP levels had significantly decreased at the sixth month after nonsurgical periodontal therapy in healthy subjects.

Matilla et al. (41) reported that after nonsurgical periodontal therapy, mean serum CRP levels declined from 1.07 to 0.7 mg/L in healthy subjects. In their 30 patients, only 6 had high CRP levels, and in agreement with Matilla et al. (41), in this study, CRP levels were elevated some of the patients with periodontitis. Of the 15 control patients, only 4 had high CRP levels. The CRP levels had decreased significantly at the third month after the nonsurgical periodontal therapy in the poorly and well controlled group and in group 2, in our study.

After the nonsurgical periodontal therapy, we determined a significant decrease in IL-6 levels in all groups at the third month. The decrease in IL-6 levels in the control group was better than the diabetic groups.D'Aiuto et al. (40) reported that a significant decrease was determined in IL-6 levels in the second and sixth months after nonsurgical periodontal therapy.

In contrast to our study, Yamazaki et al. (42) reported that improvement in periodontal health did not affect the serum levels of CRP or IL-6. Talbert et al. (43) also suggested that the nonsurgical periodontal therapy in patients with type 2 DM did not reduce the levels of systemic inflammatory mediators. Ide et al. (44) showed that 6 weeks after a 3-month control period, nonsurgical periodontal therapy did not influence CRP, TNF-α, or IL-6 levels. There is limited number of studies about the effect of periodontal therapy in DM subjects that categorized the diabetics in poorly and well controlled. Therefore we cannot discuss our results detailed.

Limitations of our study include the small numbers of our patients and relatively short follow-up time. Clarifying the effect of nonsurgical periodontal therapy on the serum level of CRP and IL-6 in poorly controlled diabetics requires further studies with larger sample sizes.

CONCLUSIONS

We concluded that improvement in periodontal health is effective on control of systemic infection via reducing serum concentrations of CRP and IL-6 in patients with poorly and well controlled type 2 diabetes with chronic periodontitis.

In addition, our findings indicated that patients with poorly controlled and well controlled DM may respond to nonsurgical periodontal therapy as well as nondiabetic patients and the effects of the nonsurgical periodontal treatment seems to be independent of the degree of diabetic status.

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