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Effects of nonsurgical periodontal therapy on C-reactive protein and serum lipids in Jordanian adults with advanced periodontitis

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Background and Objective: Data on whether periodontal therapy affects serum CRP levels are inconclusive. The aim of this study was to determine if nonsurgical periodontal therapy has any effect on CRP and serum lipid levels in patients with advanced periodontitis.

Material and Methods: Thirty-six systemically healthy patients, ≥ 40 years of age and with advanced periodontitis, were recruited for the study. Patients were randomized consecutively to one of two groups: the treatment group ($n = 18$) or the control group ($n = 18$). Treated subjects received nonsurgical periodontal therapy, which included oral hygiene instructions and subgingival scaling and root planing. Systemic levels of inflammatory markers [C-reactive protein (CRP) and the lipid profile] were measured at baseline and 3 mo after periodontal therapy.

Results: Nonsurgical periodontal therapy in the treatment group resulted in a significant reduction in the serum CRP level. The average CRP level decreased from 2.3 mg/dL at baseline to 1.8 mg/dL ($p < 0.005$) after 3 mo of periodontal therapy. The average reduction (95% confidence interval) in CRP was 0.498 (95% confidence interval = 0.265–0.731). In the treatment group, the reduction in CRP was significantly, linearly and directly correlated with the reduction in the plaque index, the gingival index and the percentage of sites with pocket depth ≥ 7 mm (Pearson correlation coefficient = 0.746, 0.425 and 0.621, respectively). Nonsurgical periodontal therapy had no effect on the lipid parameters.

Conclusion: This study demonstrated that nonsurgical periodontal therapy results in a significant reduction in the serum CRP level. The effect of this outcome on systemic disease is still unknown.

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Several epidemiological studies have shown a statistically significant modulating effect of periodontal diseases on cardiovascular diseases (1–3). In recent years, the inflammatory effects resulting from periodontal disease have been studied extensively. However, it is not yet clear whether periodontal disease is a consequence of an underlying hyperactive immune response or is an established risk factor activating systemic inflammation (4).

C-reactive protein (CRP), an acute-phase reactant, has been strongly associated with an increased risk of cardiovascular disease (5,6). Investigative data revealed that persons with periodontitis have significantly greater serum elevations of systemic markers of inflammation (CRP and interleukin-6) when compared with healthy individuals (7,8). Furthermore, accumulating evidence indicates that the severity of periodontal disease correlates with increased levels of circulating CRP (9–12); a trend of a dose–dependent relationship between circulating CRP levels and chronic periodontitis has been suggested (13). The results from intervention studies suggest that periodontal therapy lowers the serum levels of CRP, interleukin-6 and tumor necrosis factor-α (14–18). Also, a significant decrease in CRP, plasminogen activator inhibitor-1 and fibrinogen, and white cell and platelet counts were documented after full-mouth tooth extraction (19). By contrast, in other studies, no effect of periodontal treatment was observed on the CRP level (20). However, small sample sizes, noncomparable study populations and the use of different parameters to assess the effect of treatment of periodontitis and improvement in circulating CRP levels make it difficult to interpret the findings. In a recent meta-analysis on CRP and periodontitis, a modest effect of periodontal therapy in lowering the level of circulating CRP was observed (21). More prospective and interventional studies in various populations are needed to confirm this association.

To the best of our knowledge, no intervention study has addressed periodontal disease and serum inflammatory markers among Jordanians. The purpose of this study was to investigate the effect of nonsurgical periodontal therapy on the levels of the serum inflammatory marker CRP and on cholesterol levels in medically healthy individuals suffering from advanced periodontitis.

Material and methods

Study design

A randomized clinical trial was conducted among patients with advanced periodontitis. All patients with advanced periodontitis who attended the clinics in the Department of Periodontology at the Teaching Dental Health Centre at Jordan University of Science and Technology over a period of 10 mo were screened to identify those who met the strict inclusion criteria. Patients were included in this study if they met the following inclusion criteria: (i) diagnosed with advanced periodontitis; (ii) no history of systemic disease that may affect CRP, such as impaired glucose tolerance, diabetes mellitus or other endocrine diseases, nephrotic syndrome, chronic renal disease and cardiovascular disease; (iii) have at least 20 natural teeth; (iv) not pregnant women; (v) no periodontal treatment in the 6 mo prior to the study; (vi) no history of systemic antibiotic administration within the 3 mo prior to the study or any other regular medication; and (vii) no use of tobacco in the last 12 mo. Advanced periodontitis was determined using the established criteria of at least six teeth with a pocket depth of > 5 mm and loss of attachment of ≥ 3 mm in three sites of each involved tooth (22).

A total of 36 patients were diagnosed with advanced periodontitis, met the inclusion criteria and agreed to participate in this study. Patients were randomly assigned, with the use of a computer-generated table, into one of two groups: the treatment group ($n = 18$) and the control group ($n = 18$).

Interventions

Patients in the treatment group received nonsurgical periodontal therapy, including oral hygiene instructions, and scaling and root planing (SRP). Treatment was performed by the same dentist (W.A.). SRP was carried out over two or three visits and completed within 10 d of enrollment. A local anesthetic agent was used to allow subgingival debridement to be performed in a pain-free and comfortable manner. No antibiotics were prescribed to patients. The control group received no nonsurgical periodontal treatment during the study period. They were provided with oral hygiene instructions only. Upon completion of the study, all participants in the control group received nonsurgical periodontal treatment. None of the patients in the control group developed emergency dental problems during the study period.

After SRP, a professional plaque-control program was performed twice a month during the follow-up period to reinforce the oral hygiene instructions and to rescale bleeding sites. Three months after completion of periodontal therapy, all participants in both groups (treated and control) reported for a follow-up examination and blood-sample donation. All patients in both groups attended the follow-up examination, and none reported use of antibiotics during the course of the study.

Data collection

This study was approved by the Institutional Review Board of Jordan University of Science and Technology. Informed verbal consent was obtained from all participants. Personal interviews were held to collect baseline data from each participant using a pre-structured questionnaire. Socio-demographic and detailed health history information were obtained from all study participants. The same information was updated at the follow-up examination. Anthropometric measurements of each study participant, including weight and height, were recorded. Height was measured using a standard measuring rod, and body weight was taken using a mechanical flat scale. In accordance with World Health Organization (WHO) guidelines, obesity for men and women was defined as a body mass index (BMI) of

≥ 30 kg/m^2 and overweight was defined as a BMI of 25–29.9 kg/m^2 (23). Two 5-mL venous blood samples were obtained, after a 10-h fast, from all patients in both groups at baseline and follow-up periods. Blood was collected in tubes containing 3.2% sodium citrate for analysis of CRP levels and in tubes containing EDTA for analysis of total cholesterol, triglyceride (TG) and high-density lipoprotein (HDL) cholesterol. Total cholesterol, TG and HDL cholesterol were determined in the fasting blood samples using standard enzymatic-colorimetric methods, while low-density lipoprotein (LDL) was estimated using the Friedewald formula (24).

Samples taken for CRP determination were centrifuged and stored at −20°C until analyzed. Serum levels of CRP were measured with an immunoturbidimetric high-sensitivity assay (Tina-quant CRP immunoturbidimetric assay performed on a Cobas integra analyzer; Roche Diagnostics, GmbH, Mannheim, Germany for USA). The serum CRP content, determined using the Roche Diagnostics/Hitachi 912 System, was linear between 0.05 and 25.0 mg/dL and the lower limit of detection was 0.03 mg/dL.

Periodontal clinical examination and indices

The clinical examination included a full-mouth periodontal assessment. Probing pocket depth and clinical attachment level were measured at six sites (mesial, distal and the middle sites of the buccal and lingual sides) on each tooth using a Williams periodontal probe. Clinical attachment level was measured as the distance from the cemento–enamel junction to the base of the pocket. Third molars were excluded from the examination. Additional assessments of periodontal status included the plaque index (25) and the gingival index (26). These parameters were evaluated at four sites on each tooth (mesial, distal, buccal and lingual). The clinical examiner was trained and calibrated for the clinical examinations 15 d before the start of the study. Intra-examiner reproducibility assessments were carried out in probing pocket depth and clinical attachment level examinations, and were assessed by double recordings in 10 subjects. The repeat recordings were made 7 d after the first clinical examination. The correlation coefficients between the repeated measurements were 0.80 for probing pocket depth readings and 0.81 for clinical attachment level readings.

Statistical analysis

Data analysis using the Statistical Package for the Social Sciences (SPSS)® 15 for windows (SPSS Inc., Chicago, IL, USA). Shapiro–Wilks test and Kolmogorov–Smirnov test were used to check for the normality of the distribution for continuous variables. All outcome variables, including CRP and lipid parameters, met the assumption of normality. Data were described using means and standard deviation (SD). The correlation between the changes in periodontal parameters and changes in lipid parameters and in CRP were quantified using Pearson's correlation coefficient and tested for significance using the *t*-test. The paired *t*-test was used to test for the differences between measurements at baseline and after 3 mo (paired data), in each group separately. The chi-square test was used to test for significant differences between groups with respect to gender. A $p < 0.05$ was considered statistically significant.

Results

Participants' characteristics

A total of 18 patients with advanced periodontitis [mean age (SD): 46.7 (3.4) years; range, 41–53 years] received nonsurgical periodontal therapy (treatment group) and 18 patients [mean (SD): 45.5 (3.3) years; range, 41–52 years] were not treated (control group). All patients in both groups received the self-care instructions. The socio-demographic, dental, clinical and relevant characteristics of participants at baseline are shown in Table 1. At baseline, there was no significant between-group difference in age, gender, BMI, plaque index, gingival index, percentage of sites with probing pocket depth 0–3 mm, 4–6 mm or ≥ 7 mm, number of teeth present, CRP level, LDL, HDL and total cholesterol, and TG level.

At baseline, plaque index was significantly and positively correlated with CRP ($r = 0.68$) and total cholesterol ($r = 0.35$) levels. The percentage of sites with a probing depth of ≥ 7 mm was significantly correlated with CRP ($r = 0.33$) and HDL cholesterol ($r = 0.36$) levels. Other periodontal parameters were not significantly correlated with CRP and lipid parameters.

Table 1. The socio-demographic, dental, clinical and relevant characteristics of participants at baseline

Variable	Control ($n = 18$)	Treatment ($n = 18$)	*p*-Value
Age (years)	45.4 (3.3)	46.7 (3.4)	0.256
Gender, *n* (%)			1.000
Male	10 (55.6)	10 (55.6)	
Female	8 (44.4)	8 (44.4)	
Body mass index (kg/m^2)	24.8 (1.3)	25.0 (1.6)	0.633
Plaque index	1.7 (0.1)	1.7 (0.1)	0.729
Gingival index	1.7 (0.1)	1.8 (0.1)	0.118
Percentage of sites with PD 4–6 mm	59.0 (10.8)	60.8 (10.8)	0.615
Percentage of sites with PD ≥ 7 mm	3.7 (2.1)	3.5 (1.9)	0.849
Number of teeth present	27.1 (0.8)	26.9 (0.8)	0.545
C-reactive protein (mg/dL)	2.3 (0.7)	2.3 (0.7)	0.792
Low-density lipoprotein cholesterol (mM)	3.4 (0.5)	3.4 (0.5)	0.890
High-density lipoprotein cholesterol (mM)	1.4 (0.2)	1.5 (0.3)	0.803
Total cholesterol (mM)	5.4 (0.5)	5.4 (0.4)	0.632
Triglycerides (mM)	1.2 (0.3)	1.2 (0.4)	0.996

Data are given as mean (standard deviation) unless stated otherwise.
PD, probing depth.

Table 2. Changes in periodontal parameters from baseline to 3 mo of follow up in the treatment and control groups

	Control (n = 18)			Treatment (n = 18)		
Variable	Baseline	After 3 mo	p-Value	Baseline	After 3 mo	p-Value
Plaque index	1.7 (0.1)	1.7 (0.1)	0.264	1.7 (0.1)	0.2 (0.0)	< 0.005
Gingival index	1.7 (0.1)	1.7 (0.1)	0.557	1.8 (0.1)	0.3 (0.2)	< 0.005
Percentage of sites with a probing depth of 0–3 mm	59.0 (10.8)	58.8 (10.8)	0.140	60.8 (10.8)	95.4 (3.6)	< 0.005
Percentage of sites with a probing depth of 4–6 mm	37.3 (11.7) 3.7 (2.1)	37.4 (11.7) 3.8 (2.2)	0.268	35.7 (11.2) 3.5 (1.9)	4.5 (3.5)	< 0.005
Percentage of sites with a probing depth of ≥ 7 mm			0.471		0.1 (0.3)	< 0.005

Data represent means ± standard deviation (SD) for plaque index and gingival index.

Changes in periodontal parameters at follow up

In the treatment group, nonsurgical periodontal therapy resulted in a significant decrease ($p < 0.005$) in average plaque index and average gingival index, and in the percentage of sites with pocket depths of 4–6 mm and ≥ 7 mm, after 3 mo of nonsurgical periodontal therapy (Table 2). In contrast, no significant changes in these parameters were observed in the control group 3 mo after baseline assessment.

Effect of periodontal therapy on serum CRP and lipids

As shown in Table 3, nonsurgical periodontal therapy resulted in a significant reduction in the concentration of serum CRP in the treatment group. The average concentration of circulating CRP decreased from 2.3 mg/dL at baseline to 1.8 mg/dL after 3 mo of nonsurgical periodontal therapy. The average reduction in CRP was 0.498 [(95% confidence interval (CI): 0.265–0.731). This reduction in CRP was significantly, linearly and directly correlated with the reduction in the plaque index, gingival index and percentage of sites with a pocket depth of ≥ 7 mm (Pearson correlation coefficient = 0.746, 0.425 and 0.621, respectively). The nonsurgical periodontal therapy had no effect on the lipid parameters. In contrast, the control group experienced no significant changes in serum CRP and lipid parameters 3 mo after the baseline assessment.

Discussion

Several case–control studies have emphasized that patients with chronic destructive periodontal disease have increased serum CRP levels when compared with unaffected healthy control patients (7–9,27). Separate studies have explored the potential effects of periodontal treatment on circulating CRP and other surrogate markers of the vascular response (20,28). As reported in the meta-analysis of Paraskevas *et al.* (21) moderate evidence suggests that periodontal therapy lowers the level of CRP in patients with periodontal disease.

The present study is the first demonstration of a link between nonsurgical periodontal therapy and CRP in an Arabic population. The 36 Jordanians with periodontal disease were selected carefully using strict inclusion criteria to minimize the influence of possible confounders. The nonsurgical periodontal treatment protocol and 3 mo post-treatment reassessment was carried out by the same periodontist to maintain intra-rater reliability; furthermore, by performing the post-treatment reassessment 3 mo after treatment, acute fluctuations of CRP that occur immediately after periodontal therapy were avoided.

The treatment protocol resulted in a statistically significant reduction in plaque index, gingival index and percentage of sites with a probing depth of 4–6 mm or ≥ 7 mm after 3 mo of treatment. In the present study we tried to follow a protocol of nonsurgical periodontal treatment after a single session of SRP per quadrant, in favor of treating residual periodontal pockets. In one study, inadequate periodontal treatment was found to have no significant influence on systemic mediators (29). This might explain why Ide *et al.* (20), who found a 33.77% reduction in sites with probing depth of 4–6 mm following a single course

Table 3. The changes in C-reactive protein and other parameters at baseline and after 3 mo of follow up in the control and treatment groups

	Control group (n = 18)			Treatment group (n = 18)		
Variables	Baseline	After 3 mo	p-Value	Baseline	After 3 mo	p-Value
C-reactive protein (mg/dL)	2.3 (0.7)	2.4 (0.7)	0.214	2.3 (0.7)	1.8 (0.6)	< 0.005
Low-density lipoprotein cholesterol (mM)	3.4 (0.5)	3.5 (0.4)	0.250	3.4 (0.5)	3.1 (0.6)	0.054
High-density lipoprotein cholesterol (mM)	1.4 (0.2)	1.4 (0.2)	0.607	1.5 (0.3)	1.4 (0.2)	0.512
Total cholesterol (mM)	5.4 (0.5)	5.3 (0.4)	0.411	5.4 (0.4)	5.2 (0.6)	0.270
Triglycerides (mM)	1.2 (0.3)	1.2 (0.3)	0.347	1.2 (0.4)	1.2 (0.4)	0.755

of nonsurgical periodontal therapy, reported no significant effect of nonsurgical periodontal therapy on the levels of serum vascular markers.

The results of this study confirm the findings of Yamazaki *et al*. (30) who reported a strong relationship between reduction in CRP levels and improvements of periodontal health (30). The mean decrease of circulating CRP levels in our study was of the same magnitude as the differences in CRP levels reported in previous studies after nonsurgical periodontal treatment (21,31). Furthermore, D'Aiuto *et al*. (18,31) reported a significant decrease in inflammatory markers in response to periodontal therapy, and Elter *et al*. (33) showed a trend towards a reduction in serum CRP. However, their clinical trials were conducted without including control groups. In contrast, our study was designed to include a more homogenous control group.

In our study we achieved a statistical reduction in the CRP level without use of the systemic antibiotics or anti-inflammatory regimes employed in other studies (7,17,33). In addition, our nonsurgical periodontal treatment, with repeated treatment of residual bleeding periodontal pockets, suggests that maintaining a healthy periodontium by reducing signs of periodontal inflammation had a positive impact, shown as a decreased level of the serum inflammatory marker, CRP. This interpretation supports the findings of D'Aiuto *et al*. (32), which displayed a greater decrease in the CRP levels among those with better clinical responses to periodontal treatment.

Reports by Ide *et al*. (20), Yamazaki *et al*. (30), Ushida *et al*. (35) and Offenbacher *et al*. (36) failed to find a significant reduction in serum CRP after nonsurgical periodontal treatment. In the study carried out by Ide *et al*. (20), the treatment protocol of a single course of nonsurgical therapy might have been unable to eradicate all sites affected by periodontal disease, resulting, in turn, in a greater number of residual bleeding probing depths of ≥ 4 mm. Although Yamazaki *et al*. (30) reported higher CRP levels in periodontal patients at baseline, compared with healthy control patients, and a trend towards the reduction of CRP levels after nonsurgical and surgical periodontal treatments, these findings did not reach statistical significance. Comparisons with the study of Yamazaki *et al*. (30) might be misleading because the CRP level detected in Japanese periodontal patients was lower than in the populations of other developing countries (34) and in the Jordanian population. Moreover, Ushida *et al*. (35) reported that the serum CRP level did not change after periodontal treatment among a Japanese population characterized by lower CRP levels than other populations.

Our data suggest that nonsurgical periodontal therapy may lower CRP levels among healthy patients with CRP levels initially below 3 mg/dL. Our results failed to find significant differences in serum lipid markers after nonsurgical periodontal treatment, in spite of the improvement in clinical measures of periodontitis. Our findings are in line with those of D'Aiuto *et al*. (37), which showed no significant differences in serum lipid levels after 2 mo in the standard treatment group compared with the untreated group, in spite of some reduction in total and LDL cholesterol, which was present within the intensive periodontal treatment group only. Our study showed no significant changes in all lipid parameters such findings partially agrees with Tuter *et al*. (34) who showed significant increase in HDL cholestrol and no significant changes in other serum lipids (total cholestrol, LDL cholesterol, TG) showed no significant change after periodontal treatment. The inconsistency and discrepancy in the results of the previously mentioned studies underscore the need for future long-term studies of periodontal health, and of inflammatory and hemostatic markers, and the risk of cardiovascular disease.

The limitations of the present study included, but were not limited to, the relatively small number of patients in each study group and clinical application, and therefore the results should be interpreted with caution because we were performing close supervision and retreatment every 2 wk, which is not clinically feasible. Using a sample size of 18 subjects in the treatment group, the calculated power to detect a change of 0.5 units in CRP after nonsurgical treatment, assuming a common SD of 0.6, was 78%.

In summary, the current study indicated that resolution of periodontal infection after nonsurgical periodontal therapy resulted in a significant reduction in the CRP level (on average 0.5 mg/dL) among systemically healthy patients with advanced periodontal disease. Large-scale multicentre clinical trials are needed to confirm these results.

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Conflict of interest and Source of Funding

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