ORAL DISEASES

Oral Diseases (2010) 16, 648–654. doi:10.1111/j.1601-0825.2010.01668.x

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ORIGINAL ARTICLE

Short-term effects of periodontal therapy as an adjunct to anti-lipemic treatment

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OBJECTIVE: This study was conducted to assess the effect of improved periodontal health following periodontal treatment on metabolic lipid control of patients on anti-lipemic treatment.

MATERIALS AND METHODS: The study population consisted of 20 patients aged 34–62 years with diagnoses of hyperlipidemia and chronic periodontitis. All patients used statin to treat their elevated levels of low-density lipoprotein cholesterol. Blood samples were obtained for measurement of serum lipids, fasting plasma glucose, and high sensitive C-reactive protein. Periodontal parameters, including plaque index, gingival index, probing pocket depth, clinical attachment level, and percentage of bleeding on probing, were evaluated. All parameters were assessed in each subject at baseline, after 3 months as a control (at the time of periodontal treatment), and 3 months after the non-surgical periodontal treatment that included scaling and root planning.

RESULTS: All lipid parameters decreased after the periodontal treatment, but only the decreases in total cholesterol and low-density lipoprotein cholesterol levels reached statistical significance compared to baseline (P = 0.002 and P = 0.003, respectively).

CONCLUSION: Improved periodontal health may influence metabolic control of hyperlipidemia and could be considered as an adjunct to the standard measures of hyperlipidemic patient care.

Oral Diseases (2010) **16**, 648–654

Keywords: hyperlipidemia; anti-lipemic treatment; lipids; periodontal treatment

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Received 18 June 2009, revised 6 November 2009, accepted 10 November 2009

Introduction

Hyperlipidemia has gained considerable importance in prediction of individuals' risk for cardiovascular diseases (Grover *et al*, 2003), a public health problem and major cause of death in both developed and developing countries (Murray and Lopez, 1997; Ross, 1999). Hydroxymethylglutaryl coenzyme-A (HMG-CoA) reductase inhibitors, commonly known as statins, lower cholesterol levels through inhibition of cholesterol biosynthesis. They also have additional protective cardiovascular effects resulting from their anti-inflammatory properties such as inhibition of matrix metalloproteinase-9 and tumor necrosis factor-alpha (TNF-α) (Wong *et al*, 2001; Koh *et al*, 2002; Nagashima *et al*, 2002).

Periodontal disease is an infectious disease which may result in increased spillover of inflammatory cytokines from the gingival tissues into the blood circulation, leading to increased mobilization of lipids from the liver and adipose tissue (Offenbacher *et al*, 1998; Iacopino and Cutler, 2000). Lipids may interact directly with the macrophage cell membrane, interfering with membrane-bound receptors and enzyme systems, and altering macrophage gene expression for essential polypeptide growth factors and pro-inflammatory cytokines such as TNF-α and interleukin-1 beta (IL-1β) (Doxey *et al*, 1995; Chu *et al*, 1999) which are thought to be associated with periodontal disease (Stashenko *et al*, 1991; Heasman *et al*, 1993). Several studies have found that subjects with periodontal disease have higher serum levels of total cholesterol, low-density lipoprotein cholesterol (LDL) and triglycerides when compared to subjects with a healthy periodontium (Cutler *et al*, 1999; Lösche *et al*, 2000; Moeintaghavi *et al*, 2005). Also, patients diagnosed with hyperlipidemia have significantly higher values of periodontal parameters than control subjects with normal metabolic status (Noack *et al*, 2000; Fentoğlu *et al*, 2009). The interrelationship

between periodontitis and hyperlipidemia provides an example of a systemic disease predisposing to oral infection, and once the oral infection establishes, it exacerbates the systemic disease.

It has been reported that elevated values of serum lipids may lead to poor periodontal health (Noack *et al*, 2000; Katz *et al*, 2001). Yet, only one (our group's previous) study was conducted in mild to moderate hyperlipidemic patients in diet modification treatment. We found the control of periodontal infection results in significant decreases in lipid levels (Oz *et al*, 2007). Up to date, there are no data reported regarding the effects of periodontal treatment on serum lipid levels in hyperlipidemic patients on anti-lipemic treatment. Therefore, the purpose of the present study is to evaluate whether local, non-surgical periodontal treatment influences metabolic control of hyperlipidemia in hyperlipidemic patients receiving a statin group anti-lipemic agent.

Materials and methods

Subjects

This study was performed as a joint collaboration between the Internal Medicine Department at Hacettepe University and the Periodontology Department at Ankara University School of Dentistry. The study protocol was approved by the local ethics committee and was carried out in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki as revised in 2000.

Subjects were selected from patients attended to at the Hacettepe University's Internal Medicine Department for control examination. The study was conducted between April 2004 and April 2006.

The inclusion criteria were:

(1) hyperlipidemic patients prescribed statins;
(2) patients with at least 1 natural teeth in the mouth, and
(3) at least four pockets located on non-adjacent different teeth with probing pocket depth of at least 4 mm.

Exclusion criteria used were any other systemic disease affecting lipid metabolism (i.e. impaired glucose tolerance, diabetes mellitus or other endocrine diseases, nephritic syndrome, chronic renal disease, and cardiovascular disease); any current hormone replacement treatment; three-fold elevation in the liver enzymes; having received any periodontal treatment during the past 6 months, and any systemic antibiotic administration within the last 3 months. Smokers and ex-smokers were also excluded from the study. Fasting plasma glucose levels were measured in order to detect the presence of diabetes or prediabetic/metabolic syndrome, exclusionary conditions for study participation.

Twenty hyperlipidemic patients – twelve females and eight males aged 34–62 years (mean 51.85 ± 6.83) – who were prescribed a statin group anti-lipemic drug by the same physician were included in the study. A lipid-lowering diet and a physical training program were recommended initially with no further monitoring. After being informed on the purpose of the study and given ample opportunity to ask any questions, the subjects signed consent forms.

All participants were asked to respond to a questionnaire regarding their medical status, current medications, socio-demographic characteristics, and life-style habits. Data related to age, gender, body mass index (BMI) (kg m^{-2}), and the number of natural teeth present was recorded. The reason for teeth lost was evaluated according to the patients' history. BMI was calculated as body weight in kilograms divided by the square value of height in meters.

Metabolic parameters

Blood samples were collected for the measurement of triglyceride, total cholesterol, low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), very low-density lipoprotein cholesterol (VLDL), fasting plasma glucose (FPG) and high sensitive C-reactive protein (hsCRP). The samples were obtained after a 12-h fasting period from an antecubital vein. Biochemical assessments were performed in the clinical biochemistry laboratory of the Hacettepe University Hospital. Serum lipid levels were determined by using routine enzymatic methods. In order to identify subjects with pathological lipid values, the following cut-off points were used, according to the laboratory's recommendation: Triglyceride >200 mg dl^{-1}, total cholesterol >200 mg dl^{-1}, LDL >130 mg dl^{-1}, HDL <35 mg dl^{-1}, and VLDL >40 mg dl^{-1}. Nephelometric method was used to assess serum hsCRP levels. The lower and upper detection limits for CRP were 0.00 and 1.1 mg dl^{-1}, respectively.

Periodontal parameters

At baseline, dental examinations were conducted by the same clinician (ÖF). All dental variables were assessed at six different sites (mesio-buccal, mid-buccal, disto-buccal, mesio-lingual, mid-lingual, and disto-lingual) of each tooth present, including wisdom teeth. Clinical measurements of periodontal parameters were recorded on a full-mouth and included plaque index (PI) (Silness and Löe, 1964), gingival index (GI) (Löe and Silness, 1963), probing pocket depth (PPD), clinical attachment level (CAL), and bleeding on probing (BOP). All assessments were carried out with the Williams periodontal probe.

All subjects were reassessed after a 3-month period during which they received statin, but no periodontal care (3MFU) by the same clinician (ÖF).

At the end of the 3-month control period, all subjects received non-surgical periodontal treatment consisting of two appointments of intensive oral hygiene instruction, including plaque disclosing, tooth brushing technique instruction, inter-dental cleaning, and supragingival scaling and polishing as well as four appointments during 1 week during which subgingival debridement was completed on a quadrant-by-quadrant basis using hand instruments. One month following root planning, periodontal parameters were recorded to

determine any further surgical treatment needs of the study population, and site-specific rescue therapy was provided.

All periodontal parameters and systemic factors were re-examined 3 months after completion of the periodontal treatment at a 6-month follow-up visit (6MFU), i.e. after 6 months with statins treatment. The study design is illustrated in Figure 1.

Analysis of ıntra-examiner reproducibility

Reproducibility of the examiner (ÖF) was assessed by conducting duplicate clinical periodontal examinations on five patients. Each subject was assessed twice in one visit, with a 1-hour interval. The second set of recordings was carried out 'blinded' to the first assessment. Reproducibility of the examination was determined by calculation percentage of sites examined where the scores were repeated exactly or to an accuracy of ± 1 mm. Assessment of the mean difference in the scores (with 85% accuracy) between the two examinations indicated there was no systematic bias in measurements.

Statistical analysis

All data are presented as means with standard deviations and range of values. Non-parametric analysis of variance for repeated measurements (Friedman test) was used to evaluate differences between the three time points: baseline, 3-month follow-up, and 6-month follow-up. A statistical significance threshold of $P < 0.05$ was accepted. Wilcoxon signed ranks test was used for post hoc analyses ($P < 0.0167$ was accepted as significant).

Results

Two hundred and ninety-eight subjects with hyperlipidemia were evaluated, and 20 eligible patients with hyperlipidemia and chronic periodontitis were enrolled in the study. All subjects completed the entire study, and no adverse effects were reported. All patients received atorvastatin in the dosage of 10 or 20 mg at baseline. At the end of the first month, lipid levels of the subjects were re-evaluated for possible need for dose adjustment. However, no need to change the statin doses for any of the participants was identified. Thus, statin dosage of the study population was constant throughout the study. Also, all patients stated there was no problem in compliance with the prescribed statin regimen.

The mean number of sites with probing depths of at least 4 mm was 10.95 with a range of 4–16, and the mean number of different teeth with PPD ≥4 mm was 5.05 with a range of 3–9.

The average number of natural teeth was 22.10 with a range of 10–29. The mean number of teeth lost due to self-reported mobility was 1.95 with a range of 0–6.

The effects of the periodontal treatment on the periodontal variables are displayed in Table 1. For PI, GI, PPD, BOP and CAL, triad comparisons were made (Friedman, $P = 0.000$, $P = 0.000$, $P = 0.000$, $P = 0.000$ and $P = 0.116$, respectively). There were significant differences in periodontal parameters between the 3MFU and baseline except for PPD and CAL. Comparative analysis were also performed for triglyceride, total cholesterol, LDL, HDL, VLDL, FPG, CRP and BMI (Friedman, $P = 0.572$, $P = 0.002$, $P = 0.016$, $P = 0.529$, $P = 0.607$, $P = 0.368$, $P = 0.037$ and $P = 0.007$, respectively). Total cholesterol and LDL levels and BMI showed statistically significant decreases at the end of the control period ($P = 0.006$, $P = 0.022$, $P = 0.039$, respectively). There was a significant increase in serum CRP levels at the 3MFU ($P = 0.017$). The changes in the systemic parameters at each study visit are shown in Table 2.

PI, GI, PPD and BOP showed significant decreases after 6 months, compared to both baseline and 3 months (Table 1). All lipid parameters also decreased at the end of the study, but only the decreases in total cholesterol and LDL levels reached statistical significance compared to baseline ($P = 0.002$ and $P = 0.003$, respectively). A significant decrease was also found in BMI ($P = 0.013$) at the end of the study, whereas serum hsCRP levels showed a statistically significant increase ($P = 0.011$) compared to baseline (Table 2).

Discussion

The association between periodontal health and hyperlipidemia has been discussed widely in the dental literature (Pohl *et al*, 1992; Johansson *et al*, 1994; Saito *et al*, 1998; Cutler *et al*, 1999; Ebersole *et al*, 1999; Wakai *et al*, 1999; Lösche *et al*, 2000; Noack *et al*, 2000; Katz *et al*, 2001, 2002; Buhlin *et al*, 2003; Montebugnoli *et al*, 2004; Morita *et al*, 2004; Uchiumi *et al*, 2004; Maglakelidze *et al*, 2005; Moeintaghavi *et al*, 2005; Fentoğlu *et al*, 2009). Although very limited data are reported on the periodontal status of hyperlipidemic

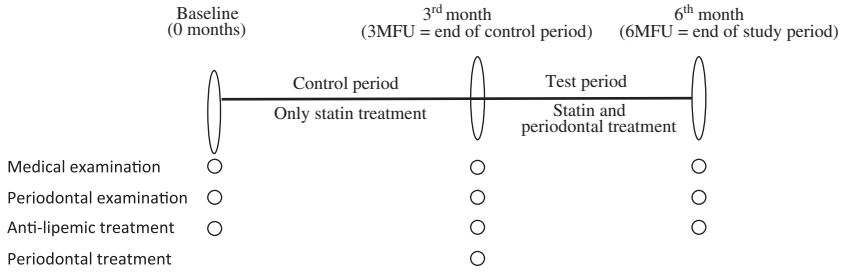

Figure 1 Scheme of study design

Table 1 Periodontal parameters at each study point: baseline, 3 months after statins only (3MFU), and at 6 months after 3 months with statins only, then periodontal treatment, followed by 3 months with statins continued (6MFU) (mean, standard deviation, and range)

	Baseline (BL) (0 months)		*After statins only (3MFU)*		*3 months after periodontal treatment (6MFU)*				
	Mean ± s.d.	*Range*	*Mean ± s.d.*	*Range*	*Mean ± s.d.*	*Range*	*3MFU/BL*	*6MFU/3MFU*	*6MFU/BL*
PI	1.92 ± 0.59	0.92–2.73	1.66 ± 0.61	0.69–2.76	0.73 ± 0.40	0.14–1.46	0.003	0.000	0.000
GI	1.18 ± 0.41	0.44–1.87	1.08 ± 0.40	0.34–1.75	0.54 ± 0.34	0.01–1.17	0.002	0.000	0.000
PPD (mm)	2.97 ± 0.60	2.26–4.46	2.87 ± 0.58	2.23–3.96	2.31 ± 0.43	1.84–3.36	NS	0.000	0.000
BOP (%)	49.02 ± 19.67	15–84	39.90 ± 18.52	11–78	19.82 ± 11.57	6–47	0.001	0.000	0.000
CAL (mm)	3.30 ± 1.63	0.65–6.64	3.14 ± 1.50	0.76–7.07	3.07 ± 1.59	0.75–7.57	NS	NS	NS

3MFU/BL = comparison of 3MFU to baseline (BL), 6MFU/3MFU = comparison of 6MFU to 3MFU, 6MFU/BL = comparison of 6MFU to baseline (BL), 3MFU = 3 months follow-up after baseline (after 3 months with statins only); 6MFU = 6 months follow-up (after 6 months with statins and 3 months after periodontal treatment); NS = not significant; PI = plaque index; GI = gingival index; PPD = probing pocket depth; BOP = bleeding on probing; CAL = clinical attachment level.

patients who underwent medical evaluation, it has been reported that hyperlipidemic patients manifested poor periodontal status compared to healthy controls (Noack *et al*, 2000; Fentoğlu *et al*, 2009). The findings in these studies seem to conclude that successful management of periodontal infection may lead to reduction in local periodontal symptoms and may have a beneficial effect on metabolic control of hyperlipidemia.

To our knowledge, this is the first study investigating the effects of a periodontal treatment on lipid levels in hyperlipidemic patients receiving anti-lipemic medication treatment. Although the study population was relatively small due to the stringent eligibility requirements involving elimination of individuals with a number of potential confounders, such as impaired glucose tolerance, diabetes mellitus and other endocrine diseases, nephritic syndrome, chronic renal disease and cardiovascular disease, which conditions are all believed to be involved in the development of both periodontal disease and hyperlipidemia.

At the beginning of the study, life-style changes, such as diet modification and physical exercise – which are important components of the treatment of lipid disorders – were recommended in addition to anti-lipemic drug treatment. All patients stated they complied with the physician's recommendations during the study, but further monitoring was not performed. Also, it was not feasible to measure fat mass during routine medical check-up. Consequently, it was decided to use the BMI as a proxy for changes in body composition. No additional guidance, such as weight loss management, was provided.

To avoid the effects of individual variations and any time-related interference on the results obtained at the end of the periodontal treatment (3MFU), both periodontal parameters and lipid markers were assessed again 3 months after the periodontal treatment during which period subjects received no periodontal care.

In our study, both periodontal parameters (PI, GI, and BOP) and lipid levels (total cholesterol and LDL) manifested statistically significant reductions after 3 months compared to baseline. The significant reductions in the periodontal parameters may be attributed to the role of the statins, which have anti-inflammatory

Table 2 Biochemical parameters at each study point: baseline, 3 months after statins only (3MFU), and at 6 months after 3 months with statins only, then periodontal treatment, followed by 3 months with statins continued (6MFU) (mean, standard deviation, and range)

	Baseline (BL) (0 months)		*After statins only (3MFU)*		*3 months after periodontal treatment (6MFU)*				
	Mean ± s.d.	*Range*	*Mean ± s.d.*	*Range*	*Mean ± s.d.*	*Range*	*3MFU/BL*	*6MFU/3MFU*	*6MFU/BL*
Triglyceride (mg dl^{-1})	168.45 ± 118.12	45–619	161.05 ± 101.80	76–531	161.40 ± 69.85	75–324	NS	NS	NS
Total cholesterol (mg dl^{-1})	246.15 ± 50.78	149–368	207.20 ± 35.56	121–252	199.60 ± 33.39	145–277	0.006	NS	0.002
LDL (mg dl^{-1})	162.46 ± 45.71	81–275	125.39 ± 37.51	57.60–184	119.36 ± 35.70	73.20–189.00	0.022	NS	0.003
HDL (mg dl^{-1})	50.02 ± 14.06	30–89.40	47.02 ± 11.99	34.30–80.00	48.16 ± 10.34	32.50–77.00	NS	NS	NS
VLDL (mg dl^{-1})	33.56 ± 23.49	9–123	32.22 ± 20.35	15–106.20	32.27 ± 14.00	14.80–64.80	NS	NS	NS
FPG (mg dl^{-1})	91.75 ± 10.16	75–123	95.25 ± 9.83	87–117	91.83 ± 8.18	76–98	NS	NS	NS
hsCRP (mg dl^{-1})	0.63 ± 1.20	0.01–5.54	0.92 ± 1.69	0.06–7.38	1.14 ± 1.71	0.03–6.21	0.017	NS	0.011
BMI (kg m^{-2})	29.30 ± 4.40	21.67–39.63	29.20 ± 4.31	21.67–39.59	29.06 ± 4.37	21.31–39.45	0.039	NS	0.013

3MFU/BL = comparison of 3MFU to baseline (BL), 6MFU/3MFU = comparison of 6MFU to 3MFU, 6MFU/BL = comparison of 6MFU to baseline (BL), 3MFU = 3 months follow-up after baseline (after 3 months with statins only); 6MFU = 6 months follow-up (after 6 months with statins and 3 months after periodontal treatment); NS = not significant; LDL = low-density lipoprotein cholesterol; HDL = high-density lipoprotein cholesterol; VLDL = very low-density lipoprotein cholesterol; FPG = fasting plasma glucose; hsCRP = high sensitive C-reactive protein; BMI = body mass index.

pleiotropic effects (Sukhova *et al*, 2002) and also to some degree to the influence of the Hawthorne effect associated with the improvement of oral hygiene as an unintended consequence of research participation (Feil *et al*, 2002). Statins are inhibitors of HMG-CoA reductase and they were developed for the reduction of serum cholesterol levels (Endo *et al*, 1976) and have been used successfully in the prevention and treatment of coronary heart disease (Shepherd *et al*, 1995; Sever *et al*, 2003). Therefore, the significant decreases in total cholesterol and LDL levels are anticipated results due to the statin regimen, but improvement in the periodontal health could also have contributed to these results.

The results obtained 3 months after the non-surgical periodontal treatment (6MFU) showed an improvement in lipid profile, even though among lipid parameters only the decreases in total cholesterol and LDL levels reached statistical significance. There were no significant differences in lipid parameters between the 3MFU and 6MFU, but when expressed as degree of significance levels (*P*-values), the decreases in total cholesterol and LDL levels are greater at the 6MFU than in 3MFU, compared to baseline. Our study population had mainly slight to moderate periodontal disease, as opposed to severe, bacteria-induced chronic periodontitis, and the change in PPD after 6 months is small. This means the positive effect observed on the lipids after periodontal treatment stems primarily from the treatment of gingivitis, representing active/acute inflammation. Although no significant difference was found in total cholesterol and LDL levels between 3MFU and 6MFU, periodontal treatment as an adjunct to anti-lipemic therapy may increase the impact of statins due to the resolution of the gingival inflammation.

Periodontitis-induced changes in immune cell function may cause metabolic dysregulation of lipid metabolism through a mechanism involving pro-inflammatory cytokines (Kinane, 1998; Iacopino and Cutler, 2000). The influence of periodontal disease on metabolism has been supported by evidence that treatment of periodontal disease improves metabolic control in people with diabetes type 2 (Grossi *et al*, 1997; Rodrigues *et al,* 2003; Skaleric *et al,* 2004; Kiran *et al*, 2005). Furthermore, periodontal infection is a source of periodic and asymptomatic bacteremia (Li *et al*, 2000; Daly *et al*, 2001), which can stimulate the release of the fat-mobilizing cytokines from the liver, such as IL-1β and TNF-α, resulting in hyperlipidemia. The ability of periodontitis to influence serum lipid levels has been demonstrated in a study in non-human primates with ligature-induced periodontitis (Ebersole *et al*, 1999).

Infections with *Chlamydia pneumoniae* and *Helicobacter pylori*, which are believed to be associated with an increased risk of cardiovascular disease, have been shown to be associated with increased plasma cholesterol and triglyceride levels (Ellis, 1997; Laurila *et al*, 1997, 1999). Uchiumi *et al* (2004) reported that subcutaneous and continuous administration of lipopolysaccharide induced hypertriglyceridemia by increasing serum triglyceride levels significantly and free fatty acid levels slightly. These findings support the hypothesis that chronic infections, including periodontitis, may modify the serum lipid profile in a way that increases the risk of atherosclerosis, and therefore, the treatment of periodontitis may result in a potential effect on metabolic control of hyperlipidemia.

Our data obtained in hyperlipidemic patients are in concordance with other studies (Pussinen *et al*, 2004; D'Aiuto *et al*, 2005; Lösche *et al*, 2005) conducted in normolipidemic subjects with periodontitis, which have shown a positive effect of periodontal treatment on serum lipid profile. Pussinen *et al* (2004) demonstrated a significant increase in the HDL/LDL ratio after periodontal treatment. Lösche *et al* (2005) reported that periodontal treatment led to slight reductions in serum lipids, although there were no significant changes in the plasma levels of different lipid fractions. In another study, subjects with severe and generalized periodontitis received intensive periodontal treatment, including standard periodontal treatment with adjunctive local delivery of minocycline, which led to decreases in total cholesterol and LDL levels 2 months following the periodontal treatment (D'Aiuto *et al*, 2005).

CRP, a lipoprotein-associated inflammatory mediator, was also evaluated in our study. Although there were significant reductions in periodontal parameters and cholesterol levels, there were significant increases in CRP levels at both 3MFU and 6MFU compared to baseline. Contrary to our results, other studies have reported significant decreases in CRP levels following periodontal treatment (D'Aiuto *et al*, 2004a,b,c, 2005). This discrepancy may stem from the differences associated with the study population. Almost all clinical studies on the effect of periodontal treatment on serum CRP levels were conducted in systemically healthy subjects, whereas we examined serum CRP levels in a study population of hyperlipidemic patients. Plasma lipoproteins are for the most part involved in the transport of acute phase reactant proteins, such as CRP, serum amyloid A, and secretory phospholipase A2, the presence and level of which greatly increase the risk of atherosclerosis (Chait *et al*, 2005). CRP is transported freely in plasma rather than bound to circulating lipoproteins, although it can interact with oxidized phospholipids and oxidized lipoproteins in vitro (Chang *et al*, 2002). CRP activates complement and binds to Fc receptors, which may facilitate the uptake and clearance of apoptotic and necrotic cells during the acute-phase response (Volanakis, 2001). In our study, while serum lipids decrease, CRP levels increase at 3 and 6 months compared to baseline. The increases in CRP levels seem to be associated with the decreases in levels of serum lipoproteins, which transport CRP, rather than with the tissue injury related to periodontal instrumentation. So the understanding of the phases involved in CRP-synthesis, CRP-binding to circulating lipoproteins, and the amount of CRP remaining free will be more significant in this study population. Therefore, both the serum level of lipid fractions and the tissue injury related to periodontal instrumentation may affect serum CRP levels in hyperlipidemic patients.

Finally, in this study among subjects with slight to moderate periodontal disease, the decrease in cholesterol

levels following periodontal treatment (at the 6MFU) seems to be slightly greater than the decrease after 3 months with only statin treatment, but no periodontal treatment, compared to baseline.

Even though further long-term studies in larger populations with more severe periodontal disease are needed to confirm the effect of periodontal treatment on serum lipid profiles in hyperlipidemic patients in anti-lipemic drug treatment, prevention and control of periodontal disease could be considered an integral part of hyperlipidemic control.

Acknowledgments

Source of funding statement: No external funding, except for the support of the authors' institutions, was received for this study.

Conflict of interest

The authors declare they have no conflict of interest.

Author contributions

Özlem Fentoglu, Tümay Sözen, S. Gül Öz, Cem A. Gürgan, and Yasar Aykaç designed the study and analyzed the data. Tümay Sözen, S. Gül Öz, Yasar Aykaç and F. Yesim Kırzıoğlu reviewed critically. Banu Kale Köroğlu, Mine Öztürk Tonguç, and Yonca Sönmez analyzed the data.

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