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# Pro-inflammatory cytokine levels in association between periodontal disease and hyperlipidaemia

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***Abstract***

**Aim:** The aim of this study was to evaluate serum and gingival crevicular fluid (GCF) pro-inflammatory cytokine levels in association between periodontal disease and hyperlipidaemia.

**Material and Methods:** One hundred and twenty-three subjects with hyperlipidaemia and 68 systemically healthy controls (C) were included in the study. Hyperlipidaemic groups were divided into two groups as suggested diet (HD) and prescribed statin (HS). Both groups were divided into three subgroups as healthy (h), gingivitis (g) and periodontitis (p). The clinical periodontal parameters, fasting venous blood and GCF samples were obtained, and serum tumour necrosis factor-alpha (TNF-α), interleukin (IL)-1β (IL-1β) and IL-6 levels were evaluated.

**Results:** The ratio of total cholesterol to high-density lipoprotein (TC/HDL) was associated with gingival index and percentage of bleeding on probing (BOP%) in both hyperlipidaemic groups. In HS group, GCF and serum IL-6 were positively correlated with BOP% and TC/HDL. GCF TNF-α was positively associated with probing pocket depth and clinical attachment level, whereas serum TNF-α was associated with BOP% in the HD group. Serum and GCF TNF-α and IL-1β were significantly associated with TC/HDL in the HD group.

**Conclusions:** Serum pro-inflammatory cytokines may play an important role in the association between periodontal disease and hyperlipidaemia.

Key words: hyperlipidaemia; IL-1β; IL-6; periodontal disease; TNF-α

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Periodontal diseases are a group of infectious diseases caused by predominantly gram-negative, anaerobic bacteria that induce local and systemic elevations of pro-inflammatory cytokines; such as tumour necrosis factor-alpha (TNF-α), interleukin (IL)-1β (IL-1β) and IL-6 (Page 1991, Page & Kornman 1997) leading to an increased mobilization of lipids from the liver and adipose tissue (Iacopino & Cutler 2000).

**Conflict of interest and source of funding statement**

The authors declare that they have no conflict of interests.

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Atherosclerotic cardiovascular disease is one of the primary causes of death in both developed and developing countries (Mehra 2007). Atherosclerosis is an inflammatory process, which initiates following the focal accumulation of lipids into the arterial intima. Thus, the role of serum lipids comes into question in this inflammatory process (Ross 1999). It has been proposed for several decades that infections may be responsible for the accelerated development of atherosclerosis (Danesh et al. 1997, Hanson 2005). Recent studies have pointed out a possible association between periodontal infection and an increased risk for cardiovascular disease (Blaizot et al. 2009, Tonetti 2009). Additionally, periodontitis and cardiovascular disease may share common risk factors, such as smoking, diabetes,

behavioural factors, aging and male gender (DeStefano et al. 1993, Beck et al. 1998, Joshipura et al. 1998).

Some reports stated that lipids may interact directly with the macrophage cell membrane, interfering with membrane-bound receptors and enzyme systems, altering macrophage gene expression for essential polypeptide growth factors and pro-inflammatory cytokines such as TNF-$\alpha$ and IL-1$\beta$ (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 (TC), low-density lipoprotein cholesterol (LDL) and triglyceride (TRG) when compared with subjects with a healthy periodontium (Cutler et al. 1999, Lösche et al. 2000, Moeintaghavi et al. 2005). Additionally, patients diagnosed with hyperlipidaemia have significantly higher values of periodontal parameters than control subjects with a normal metabolic status (Noack et al. 2000, Fentoğlu et al. 2009, Awartani & Atassi 2010). Recently, it was also stated that salivary lysosome was more closely associated with the lipid components of the metabolic syndrome (Qvarnstrom et al. 2010).

These results led the current researchers to consider that the inter-relationship between periodontitis and hyperlipidaemia may provide an example of a systemic disease predisposing to oral infection, and once the oral infection is established, it exacerbates the systemic disease.

Alterations in major inflammatory mediator levels in gingival crevicular fluid (GCF) and serum may at least partly play a role in the interactions of these two diseases. To the current authors knowledge, there are currently no published studies on GCF and serum levels of pro-inflammatory cytokines in the association between periodontal disease and hyperlipidaemia. In this context, this study aimed to evaluate the GCF and serum levels of TNF-$\alpha$, IL-1$\beta$ and IL-6 to clarify the possible link between periodontal disease and hyperlipidaemia.

## Material and Methods

### Study population

This present study was performed as a joint collaboration between the Department of Internal Medicine of Süleyman Demirel University, Faculty of Medicine and the Department of Periodontology of Süleyman Demirel University, Faculty of Dentistry. The study protocol was approved by the local ethical committee (Date: 5 December 2006, Number: 09/11) and was carried out in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki, as revised in 2000. The inclusive enrollment dates of this study were from July 2007 to July 2009.

Hyperlipidaemic patients were selected from patients attending the Süleyman Demirel University's Internal Medicine Department for routine control examination. The cases included hyperlipidaemic patients with a prescribed diet (HD) or with a statin group antilipaemic drug (HS). The controls (C) were selected from systemically healthy subjects attending the Süleyman Demirel University's Periodontology Department for dental or periodontal complaints. All of the controls were subjected to detailed systemic examinations, rather than personal declarations of health, to determine the individual's medical status via evaluation of biochemical analyses including in plasma lipid profile, glucose level, liver enzymes and thyroid tests. Subjects having at least 18 natural teeth in the mouth were incorporated into the study.

Exclusion criteria used were any other systemic disease affecting lipid metabolism (i.e. impaired glucose tolerance, diabetes mellitus, metabolic syndrome or other endocrine diseases, nephritic syndrome, chronic renal disease and cardiovascular disease); any anti-lipaemic drug treatment for more than 1 month; any current hormone replacement treatment; three-fold elevation in the liver enzymes; having received any periodontal treatment within the last 6 months; and any systemic antibiotic administration within the last three months. Smokers and ex-smokers were also excluded from the study.

### Periodontal parameters

Dental examinations were conducted by the same clinician (Ö. F.). 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, excluding wisdom teeth. Clinical measurements of periodontal parameters included plaque index (Silness & Löe 1964), gingival index (GI) (Löe & Silness 1963), probing pocket depth (PPD), clinical attachment level (CAL) and percentage of bleeding on probing (BOP%). All assessments were carried out using the Williams periodontal probe.

After the periodontal measurements were taken and radiologically supported with oral pantomographs, the patients were divided into three groups as periodontal healthy (h), gingivitis (g) and chronic periodontitis (p). The diagnosis was based on the clinical and radiographic criteria stated and described on the 1999 Consensus Classification of Periodontal Diseases (Armitage 1999) as follows:

- Periodontal healthy (h): the mean of $GI < 1$ and the mean of the percentage of $BOP \leqslant 25\%$, but with no sites of attachment loss.
- Gingivitis (g): at least two teeth with two or more sites with $BOP \geqslant 25\%$ and $GI > 1$, but with no sites of attachment loss related to chronic inflammatory periodontal disease.
- Chronic periodontitis (p): at least four teeth with a $PPD \geqslant 5$ mm, with $CAL \geqslant 2$ mm at the same time (Armitage 1999).

### Analysis of intra-examiner reproducibility

Reproducibility of the examiner (Ö. F.) was assessed by carrying out clinical periodontal data collection on five patients. Each subject was assessed twice in one visit, over a 1-h interval. The second set of measurements was carried out masked to the first assessment. Reproducibility of the data collection was determined for each site by calculation of the percentage of the sites examined where the scores were identical or within $\pm 1$ mm. Assessment of the mean difference in the scores (with 85% accuracy) between visits indicated that there was no systematic bias in the measurements between visits.

### Metabolic parameters

Blood samples were collected to measure TRG, TC, LDL, high-density lipoprotein cholesterol (HDL) and very-low-density lipoprotein cholesterol (VLDL). 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 Süleyman Demirel 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: TRG > 200 mg/dl, TC > 200 mg/dl, LDL > 130 mg/dl, HDL < 35 mg/dl and VLDL > 40 mg/dl. For HD group, plasma LDL values were < 160 mg/dl and > 130 mg/dl. For the HS group, plasma LDL values were > 160 mg/dl (Grundy et al. 2004).

Conclusively, the current study population was made up of three main groups (C, HD and HS) and their subgroups (h, g and p) as follows:

(1) systemically and periodontal healthy (Ch);
(2) systemically healthy and gingivitis (Cg);
(3) systemically healthy and chronic periodontitis (Cp);
(4) diet-suggested hyperlipidaemic and periodontal healthy (HDh);
(5) diet-suggested hyperlipidaemic and gingivitis (HDg);
(6) diet-suggested hyperlipidaemic and chronic periodontitis (HDp);
(7) statin-prescribed hyperlipidaemic and periodontal healthy (HSh);
(8) statin-prescribed hyperlipidaemic and gingivitis (HSg);
(9) statin-prescribed hyperlipidaemic and chronic periodontitis (HSp).

#### Serum samples and laboratory analysis

Blood samples from subjects were collected in vacutainer tubes. They were centrifuged at 2500 *g* for 4 min. to separate the serum. Serum aliquots were stored at − 80°C until laboratory analysis. The levels of IL-1$\beta$, IL-6 and TNF-$\alpha$ were determined using commercially available ELISA kits (Orgenium, Vantaa, Finland) for the serum. The lower limits of detection were < 7 pg/ml, < 2 pg/ml and < 9 pg/ml, for IL-1$\beta$, IL-6 and TNF-$\alpha$, respectively. The intra- and inter-assay coefficients of variations for IL-1$\beta$ were 7% and 7%, and for IL-6 were 9.4% and 8.6%, for TNF-$\alpha$ were 6% and 4%, respectively.

#### GCF samples

For periodontal healthy and gingivitis patients, GCF samples were collected from a mesio-buccal and disto-palatal site on each of three teeth in each quadrant of subjects (molar, pre-molar, canine/incisor). For periodontitis patients, the mentioned teeth groups (molar, premolar, canine/incisor) were used. However, from these teeth groups, the deepest sites were chosen for GCF sampling. The samples were obtained before clinical measurements and between the hours of 08:00 and 10:00 in the morning. The area was isolated with cotton rolls to eliminate saliva contamination and slightly air dried. The samples were obtained over 30 s with standard paper strips Periopaper®, (Proflow Inc., Amityville, NY, USA) using the orifice method, and volume was measured using a pre-calibrated Periotron 8000 (Oroflow Inc., Plainview, NY, USA). The sampling was performed before periodontal probing and clinical measurement. Care was taken to avoid mechanical injury. Strips contaminated with blood were discarded. Paper strips with absorbed GCF were placed in microcentrifuge tubes containing phosphate-buffered saline (pH 7). Tubes were vortexed and centrifuged at 1500 *g* for 10 min. The supernatants were transferred into eppendorf tubes and stored at − 80°C until analysis. Samples were thawed and assayed immediately to ensure minimal deterioration, and samples of each patient were assayed at the same time as the matched control samples.

#### Statistical analysis

Power analysis and sample size estimation were performed. The sample size ($n$): 191 (123 subjects with hyperlipidaemia and 68 subjects with systemically healthy), significance level ($\alpha$): 0.05, standardized difference ($d$): 0.50 and the statistical power of this study was found above 85% to detect the differences of the clinical periodontal parameters, and the serum and GCF cytokine levels among the study groups. There was also sufficient power in the subgroup analyses (above 85%) (NCSS/PASS, 2000 Dawson Edition, Kaysville, UT, 2000).

SPSS for Windows (version 11.0) was used for statistical evaluation of the present data. The normality of data distribution was examined using the Kolmogorov–Simirnov test. The differences between the groups of normally distributed variables were assessed using one-way ANOVA and $t$-tests. Levene's test of homogeneity of variance were performed. The Kruskall–Wallis test was used to detect the differences in the parameters among the subgroups. The Mann–Whitney $U$-test with Bonferroni's correction was used to compare the differences among the subgroups. A value of $p < 0.01$ was accepted to be significant. Correlations between serum markers (lipids and cytokines) and clinical periodontal parameters were determined by Pearson's correlation analyses. Bivariate correlation coefficients were estimated. A value of $p < 0.05$ was considered to be significant.

## Results

One hundred and twenty-three subjects with hyperlipidaemia aged 30–57 (60 females and 63 males) and 68 systemically healthy controls aged 31–54 (37 females and 31 males) participated in the current study. Significant differences in age and gender (matching variables) ($p > 0.05$) were not observed. Fifteen patients in the HS group (five patients for each subgroups of HS group) received atorvastatin in the dosage of 10 or 20 mg. The number of hypertensive patients were 6 and 8 for the diet and statin groups, respectively. For the hyperlipidaemic groups, BMI value was ranged from 16.73 to 43.97, and for the systemically healthy group BMI value was ranged from 17.84 to 38.20. The HDp and HSp groups had higher BMI value in comparison with the Cp group ($p < 0.05$ and $p < 0.01$, respectively).

Table 1 displays the clinical periodontal variables in the study groups. The inter-group statistical comparisons of clinical periodontal parameters of study groups are shown in Table 2. The median values for GI, PPD, BOP% and CAL in the HSg group were statistically significantly higher than those of the HDg and Cg groups. The HSp group had a higher value of BOP% when compared with the Cp and HDp groups ($p < 0.001$ and $p < 0.01$, respectively).

Table 3 shows the serum lipid parameters of the study groups. The Cg group showed a higher serum TC/HDL ratio and LDL levels than the Ch group ($p < 0.0167$). The HDg and HDp groups had higher serum TC and LDL levels in comparison with the HDh group ($p < 0.0167$).

The TNF-$\alpha$, IL-1$\beta$ and IL-6 levels in the serum and GCF samples of the study groups are presented in Table 4. The inter-group statistical comparisons of

*Table 1*. Clinical periodontal parameters of study groups [median (min–max)]

| Groups | C ($n = 68$) | | | HD ($n = 66$) | | | HS ($n = 57$) | | |
|---|---|---|---|---|---|---|---|---|---|
| Subgroups | Ch ($n = 20$) | Cg ($n = 20$) | Cp ($n = 28$) | HDh ($n = 17$) | HDg ($n = 20$) | HDp ($n = 29$) | HSh ($n = 16$) | HSg ($n = 18$) | HSp ($n = 23$) |
| PI | 1.09 (0.10–2.75) | 1.31 (0.15–3.00) | 2.07 (0.68–3.00) | 1.17 (0.16–2.58) | 1.51 (0.36–2.65) | 1.17 (0.30–2.89) | 0.98 (0.21–2.82) | 1.00 (0.18–2.56) | 1.38 (0.58–2.84) |
| GI | 0.54 (0.12–1.67) | 0.67 (0.20–1.45) | 1.12 (0.35–2.58) | 0.56 (0.21–2.43) | 0.92 (0.44–1.57) | 0.91 (0.33–2.21) | 0.83 (0.14–1.28) | 1.08 (0.50–2.54) | 1.00 (0.35–2.00) |
| PPD (mm) | 1.90 (1.00–2.56) | 2.00 (1.12–2.52) | 2.74 (1.10–4.07) | 1.73 (1.00–2.40) | 2.00 (1.10–2.64) | 3.07 (1.16–7.13) | 2.11 (1.03–2.52) | 2.24 (1.69–4.00) | 2.920 (1.77–3.87) |
| BOP (%) | 7.91 (1.66–9.05) | 32.50 (0.53–100) | 50.02 (8.38–100) | 9.85 (7.00–10.22) | 33.30 (12.82–100) | 52.18 (3.44–100) | 9.72 (2.38–11.80) | 38.09 (7.13–66.66) | 91.50 (0.60–100) |
| CAL (mm) | 1.90 (1.00–2.56) | 2.00 (1.12–2.52) | 3.17 (1.16–7.13) | 1.73 (1.00–2.40) | 2.68 (1.10–2.94) | 3.15 (1.25–4.38) | 1.92 (1.03–2.52) | 2.84 (1.69–4.00) | 3.34 (1.21–4.89) |

C, systemically healthy control group; HD, diet-suggested hyperlipidaemic group; HS, statin-prescribed hyperlipidaemic group; Ch, systemically and periodontal healthy group; Cg, systemically healthy and gingivitis group; Cp, systemically healthy and periodontitis group; HDh, diet-suggested hyperlipidaemic and periodontal healthy group; HDg, diet-suggested hyperlipidaemic and gingivitis group; HDp, diet-suggested hyperlipidaemic and periodontitis group; HSh, statin-prescribed hyperlipidaemic and periodontal healthy group; HSg, statin-prescribed hyperlipidaemic and gingivitis group; HSp, statin-prescribed hyperlipidaemic and periodontitis group; PI, plaque index; GI, gingival index; PPD, probing pocket depth; BOP, bleeding on probing; CAL, clinical attachment level.

*Table 2*. Inter-group statistical comparisons of clinical periodontal parameters of study groups

| | Group | Mann–Whitney *U* |
|---|---|---|
| | | *p* value |
| PI | Ch *versus* HDh | 0.045 |
| GI | HSg *versus* Cg | 0.005* |
| | HSg *versus* HDg | 0.002* |
| PPD (mm) | HSg *versus* Cg | 0.003* |
| | HSg *versus* HDg | 0.002* |
| BOP (%) | HSg *versus* Cg | 0.001* |
| | HSg *versus* HDg | 0.002* |
| | HSp *versus* Cp | 0.000** |
| | HSp *versus* HDp | 0.001* |
| CAL (mm) | HSg *versus* Cg | 0.002* |

*$p < 0.01$.
**$p < 0.001$.
Ch, systemically and periodontal healthy group; Cg, systemically healthy and gingivitis group; Cp, systemically healthy and periodontitis group; HDh, diet-suggested hyperlipidaemic and periodontal healthy group; HDg, diet-suggested hyperlipidaemic and gingivitis group; HDp, diet-suggested hyperlipidaemic and periodontitis group; HSh, statin-prescribed hyperlipidaemic and periodontal healthy group; HSg, statin-prescribed hyperlipidaemic and gingivitis group; HSp, statin-prescribed hyperlipidaemic and periodontitis group; PI, plaque index; GI, gingival index; PPD, probing pocket depth; BOP, bleeding on probing; CAL, clinical attachment level.

serum and GCF parameters of study groups are shown in Table 5. The GCF level of IL-6 was significantly higher in the HSp group when compared with both the Cp and HDp groups ($p < 0.01$).

The significant correlations between clinical periodontal parameters and biochemical data are shown in Table 6. In the hyperlipidaemic groups, the TC/HDL ratio was significantly associated with GI and BOP% ($p < 0.05$). Serum HDL, LDL and VLDL levels were also significantly correlated with GI in the HS group ($p < 0.01$, $p < 0.05$ and $p < 0.05$, respectively). In the HD group, PPD was negatively correlated with HDL ($p < 0.05$). GCF TNF-$\alpha$ level was positively correlated with PPD and CAL ($p < 0.05$), whereas serum TNF-$\alpha$ level was correlated with BOP% ($p < 0.05$), in the HD group. Serum TNF-$\alpha$ and IL-$\beta$ levels were correlated with the TC/HDL ratio in the HD group ($p < 0.01$ and $p < 0.05$, respectively). GCF TNF-$\alpha$ and IL-$\beta$ levels were also associated with the TC/HDL ratio in the HD group ($p < 0.05$).

In the HS group, GCF and serum IL-6 levels were positively correlated with BOP% ($p < 0.01$ and $p < 0.05$, respectively). The TC/HDL ratio showed significant correlations with serum and GCF IL-6 levels in the HS group ($p < 0.01$ and $p < 0.05$, respectively).

## Discussion

In this study, serum and GCF pro-inflammatory cytokine levels were evaluated in the association between periodontal disease and hyperlipidaemia. There are several studies regarding the association between periodontal disease and serum lipids. However, these studies have almost all been conducted in systemically healthy subjects with periodontitis (Cutler et al. 1999, Lösche et al. 2000, Moeintaghavi et al. 2005); and there are very limited data regarding the periodontal status of hyperlipidaemic subjects. Only the studies of Noack et al. (2000), Awartani & Atassi (2010), and a previous study by the current authors (Fentoğlu et al. 2009) reported an association between periodontal status and serum lipids in the hyperlipidaemic population.

This present study is believed to be the first study investigating the potential role of pro-inflammatory cytokines in the relationship between periodontal disease and hyperlipidaemia. In this current study, to eliminate the confounding factors that affect lipid metabolism, strict inclusion criteria for the groups of this study population were followed and a homogenous hyperlipidaemic population was attempted through a definitive diagnosis by the physician and through the elimination of potential shared confounders, such as impaired glucose tolerance, smoking, diabetes mellitus, cardiovascular disease, etc., which are all conditions believed to be involved in the development and/or progression of both periodontal disease and hyperlipidaemia. Furthermore, subgroups (periodontal healthy, gingivitis and periodontitis) were composed according to the periodontal status of the both hyperlipidaemic and systemically healthy subjects to

*Table 3.* Serum lipid parameters of study groups [median (min–max)]

| Groups | C ($n = 68$) | | | | HD ($n = 66$) | | | | HS ($n = 57$) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Subgroups | Ch ($n = 20$) | Cg ($n = 20$) | Cp ($n = 28$) | $p$ value | HDh ($n = 17$) | HDg ($n = 20$) | HDp ($n = 29$) | $p$ value | HSh ($n = 16$) | HSg ($n = 18$) | HSp ($n = 23$) | $p$ value |
| TC/HDL | 3.14 (2.46–5.59) | 4.08 (2.34–6.29) | 3.51 (2.08–4.74) | 0.015* | 5.07 (3.79–7.25) | 5.11 (3.31–7.16) | 5.25 (3.15–7.45) | | 4.79 (3.33–6.20) | 4.00 (2.87–8.14) | 4.65 (2.96–9.00) | |
| TC (mg/dl) | 146.50 (113–191) | 170.00 (140.00–197.00) | 164.00 (92.00–200.00 | | 207.00 (176–241) | 221.00 (202.00–249.00) | 220.50 (129.00–273.00) | 0.015† 0.016‡ | 222.50 (165.00–290.00) | 235.00 (155–301) | 219.00 (143.00–347.00) | |
| LDL (mg/dl) | 77.50 (52.40–126.40) | 102.00 (66.00–124.60) | 96.50 (31.80–124.40) | 0.005* | 131.40 (105.00–168.00) | 150.80 (59.00–170.00) | 150.00 (59.00–192.80) | | 133.00 (73.60–263.20) | 144.80 (82.00–189.60) | 146.90 (78.60–216.00) | |
| HDL (mg/dl) | 45.50 (32.00–59.00) | 41.00 (31.00–62.00) | 48.00 (33.00–71.00) | | 42.00 (30.00–69.00) | 40.00 (28.00–53.00) | 43.00 (31.00–62.00) | | 47.50 (35.00–67.00) | 56.00 (36.00–79.00) | 45.00 (29.00–68.00) | |
| VLDL (mg/dl) | 19.30 (9.80–54.00) | 22.80 (14.00–41.00) | 17.40 (8.00–43.20) | 0.002§ | 27.00 (13.00–99.40) | 30.20 (16.20–57.40) | 25.00 (10.20–74.00) | | 26.50 (11.60–86.20) | 30.20 (12.00–110.80) | 23.30 (9.00–147.00) | |
| TRG (mg/dl) | 96.50 (43.00–257.00) | 110.00 (68.00–200.00) | 86.00 (40.00–206.00) | 0.003§ | 149.00 (67.00–215.00) | 142.00 (81.00–287.00) | 125.00 (51.00–365.00) | | 132.50 (58.00–353.00) | 151.00 (64.00–554.00) | 119.00 (45.00–686.00) | |

*Comparison of Cg and Ch.
†Comparison of HDg and HDh.
‡Comparison of HDp and HDg ($p < 0.0167$).
§Comparison of Cg and Cp.
C, systemically healthy control group; HD, diet-suggested hyperlipidaemic group; HS, statin-prescribed hyperlipidaemic group; Ch, systemically and periodontal healthy group; Cg, systemically healthy and gingivitis group; Cp, systemically healthy and periodontitis group; HDh, diet-suggested hyperlipidaemic and periodontal healthy group; HDg, diet-suggested hyperlipidaemic and gingivitis group; HDp, diet-suggested hyperlipidaemic and periodontitis group; HSh, statin-prescribed hyperlipidaemic and periodontal healthy group; HSg, statin-prescribed hyperlipidaemic and gingivitis group; HSp, statin-prescribed hyperlipidaemic and periodontitis group; TC, total cholesterol; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; VLDL, very-low-density lipoprotein cholesterol; TRG, triglyceride.

evaluate serum pro-inflammatory cytokine levels in association between periodontal disease and hyperlipidaemia.

The TC/HDL ratio has been suggested to be more predictable for the determination of cardiovascular risk (Naito 1985). According to the current results, there were significant positive correlations between GI values and the TC/HDL ratio. In fact, it may be thought that hypercholesterolemia is pathognomic for periodontal disease, especially for gingivitis, because a cholesterol-rich diet may lead to subendothelial damage and increase the permeability of the basal membrane (Maglakelidze et al. 2005). In agreement with this suggestion, the TC/HDL ratio showed an increase in the systemically healthy group with gingivitis in the present study.

Systemically healthy subjects with gingivitis had a higher TC/HDL ratio and VLDL and TRG levels when compared with periodontal healthy subjects and periodontitis patients. In this context, the current results are supported by the data which emphasizes periodontal disease being associated with serum cholesterol levels (Wakai et al. 1999, Katz et al. 2001, 2002). It has also been reported that there is a relationship between periodontal disease and both cholesterol and TRG levels (Lösche et al. 2000). These findings also seemed to confirm the role of serum TRG levels in the association between periodontal disease and serum lipids (Cutler et al. 1999, Morita et al. 2004). Likewise, different from the methodology of the present study, other researchers have interpreted the association of periodontal disease and serum lipids in study populations who were not diagnosed with hyperlipidaemia, via a detailed systemic examination and did not categorize patients' periodontal conditions (periodontal healthy, gingivitis and periodontitis). Thus, the interpretations based on those studies may lead to incompatibility of the results. This means that the methodological differences (systemic and periodontal characteristics of study populations, etc.) may affect not only the serum lipid fraction (cholesterol or triglyceride) and periodontal status but also the determination of the bidirectional relationship between periodontal disease and lipid profile.

In the current study, BOP% was significantly higher in HSp group than both the HDp and Cp groups, although there were no significant differences among

*Table 4*. Serum and GCF cytokine parameters of study groups [median (min–max)]

| Groups | C ($n = 68$) | | | | HD ($n = 66$) | | | | HS ($n = 57$) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Subgroups | Ch ($n = 20$) | Cg ($n = 20$) | Cp ($n = 28$) | $p$ value | HDh ($n = 17$) | HDg ($n = 20$) | HDp ($n = 29$) | $p$ value | HSh ($n = 16$) | HSg ($n = 18$) | HSp ($n = 23$) | $p$ value |
| Serum (pg/ml) | | | | | | | | | | | | |
| TNF-$\alpha$ | 25.08 (0.71–1459.76) | 31.03 (4.98–164.89) | 14.82 (1.80–177.74) | | 32.56 (1.95–288.62) | 34.95 (1.95–1716.12) | 15.07 (1.80–732.66) | | 35.67 (2.62–212.21) | 27.08 (2.92–1437.25) | 18.38 (2.62–1792.51) | |
| IL-1$\beta$ | 2.44 (0.71–27.07) | 4.91 (0.80–36.27) | 2.94 (0.80–26.08) | | 2.22 (0.63–12.86) | 8.09 (1.36–64.54) | 6.52 (0.73–31.40) | 0.015* | 2.26 (1.51–56.95) | 6.26 (2.01–21.59) | 2.36 (0.63–30.25) | 0.011† |
| IL-6 | 5.40 (3.20–22.70) | 7.29 (3.68–37.05) | 5.82 (3.51–62.53) | 0.006‡ | 5.07 (0.01–28.68) | 6.12 (3.20–48.77) | 7.26 (3.51–122.28) | | 6.20 (3.45–23.55) | 6.36 (4.07–50.59) | 8.02 (0.59–126.44) | |
| GCF (pg/ml) | | | | | | | | | | | | |
| TNF-$\alpha$ | 0.3 (0.1–1.21) | 0.43 (0.10–5.98) | 0.52 (0.52–0.52) | | 0.34 (0.10–2.65) | 0.61 (0.1–5.86) | 2.42 (2.42–2.42) | | 0.46 (0.13–1.24) | 0.31 (0.24–0.39) | 0.57 (0.1–4.23) | |
| IL-1$\beta$ | 2.10 (0.98–7.22) | 2.10 (0.98–72.26) | 2.11 (0.54–63.49) | | 2.85 (0.98–61.64) | 4.69 (1–296.07) | 2.35 (0.98–100.27) | 0.001* | 2.98 (0.95–245.55) | 5.09 (2.08–116.3) | 3.91 (1.16–62.2) | |
| IL-6 | 1.22 (0.68–1.74) | 0.92 (0.66–1.45) | 0.92 (0.52–2.47) | | 1.25 (0.74–2.90) | 1.17 (1.08–1.25) | 1.07 (0.99–1.15) | | 0.95 (0.66–1.88) | 1.22 (0.68–1.74) | 1.48 (1.02–1.95) | |

*Comparison of HDg and HDh.
†Comparison of HSg and HSh ($p < 0.0167$).
‡Comparison of Cg and Ch,
C, systemically healthy control group; HD, diet-suggested hyperlipidaemic group; HS, statin-prescribed hyperlipidaemic group; Ch, systemically and periodontal healthy group; Cg, systemically healthy and gingivitis group; Cp, systemically healthy and periodontitis group; HDh, diet-suggested hyperlipidaemic and periodontal healthy group; HDg, diet-suggested hyperlipidaemic and gingivitis group; HDp, diet-suggested hyperlipidaemic and periodontitis group; HSh, statin-prescribed hyperlipidaemic and periodontal healthy group; HSg, statin-prescribed hyperlipidaemic and gingivitis group; HSp, statin-prescribed hyperlipidaemic and periodontitis group; GCF, gingival crevicular fluid; TNF-$\alpha$, tumour necrosis factor-alpha; IL-1$\beta$, interleukin-1$\beta$, IL-6, interleukin-6.

*Table 5*. Inter-group statistical comparisons of serum and GCF parameters of study groups

| | Groups | Mann–Whitney $U$ $p$ value |
|---|---|---|
| Serum (pg/ml) | | |
| TNF-$\alpha$ | HDg *versus* Cg | 0.016 |
| | HSg *versus* HDg | 0.032 |
| IL-1$\beta$ | HDg *versus* Cg | 0.015 |
| | HSg *versus* HDg | 0.045 |
| IL-6 | HSp *versus* HDp | 0.036 |
| | HSp *versus* Cp | 0.013 |
| GCF (pg/ml) | | |
| TNF-$\alpha$ | HDg *versus* Cg | 0.036 |
| | HSg *versus* HDg | 0.025 |
| IL-1$\beta$ | HDg *versus* Cg | 0.005* |
| | HSg *versus* HDg | 0.006* |
| | HSg *versus* Cg | 0.002* |
| IL-6 | HSp *versus* HDp | 0.003* |
| | HSp *versus* Cp | 0.001* |
| | HSg *versus* HDg | 0.004* |
| | HSg *versus* Cg | 0.003* |

*$p < 0.01$.
Ch, systemically and periodontal healthy group; Cg, systemically healthy and gingivitis group; Cp, systemically healthy and periodontitis group; HDh, diet-suggested hyperlipidaemic and periodontal healthy group; HDg, diet-suggested hyperlipidaemic and gingivitis group; HDp, diet-suggested hyperlipidaemic and periodontitis group; HSh, statin-prescribed hyperlipidaemic and periodontal healthy group; HSg, statin-prescribed hyperlipidaemic and gingivitis group; HSp, statin-prescribed hyperlipidaemic and periodontitis group; GCF, gingival crevicular fluid; TNF-$\alpha$, tumour necrosis factor-alpha; IL-1$\beta$, interleukin-1$\beta$, IL-6, interleukin-6.

periodontitis groups regarding other clinical periodontal parameters. This result may be interpreted that the degree of the deterioration of lipid metabolism may be associated with periodontitis when taking into consideration the inflammatory components of both periodontitis and hyperlipidaemia.

According to the present results, comparisons of the clinical periodontal parameters among the three groups (C, HD and HS) indicate increases in the gingivitis groups when compared with periodontitis groups, which may be attributed to the role of inflammation in lipid metabolism rather than infection. The current periodontitis groups had mainly slight-to-moderate periodontitis. Therefore, it may be thought that the severity and activity of the periodontal disease may also assist in these present results.

It has been well demonstrated that cytokines are considered to play a key role in the inflammation process (Offenbacher et al. 1986, Genco et al. 2002,

*Table 6*. Significant correlations between the clinical periodontal parameters and serum parameters in study groups

| Groups | C ($n = 68$) | | HD ($n = 66$) | | HS ($n = 57$) | |
|---|---|---|---|---|---|---|
| | *r* | *p* | *r* | *p* | *r* | *p* |
| GI-GCF IL-6 | 0.290* | 0.017 | | | | |
| GI-TC/HDL | | | 0.565* | 0.015 | 0.302* | 0.022 |
| BOP%-TC/HDL | | | 0.280* | 0.034 | 0.268* | 0.036 |
| PPD-HDL | | | −0.565* | 0.015 | | |
| PPD-serum IL-1$\beta$ | | | 0.556* | 0.017 | | |
| BOP%-serum TNF-$\alpha$ | | | 0.280* | 0.039 | | |
| PPD-GCF TNF-$\alpha$ | | | 0.330* | 0.010 | | |
| CAL-GCF TNF-$\alpha$ | | | 0.296* | 0.022 | | |
| TC/HDL-serum IL-1$\beta$ | | | 0.396* | 0.036 | | |
| TC/HDL-GCF IL-1$\beta$ | | | 0.210* | 0.035 | | |
| TC/HDL-serum TNF-$\alpha$ | | | 0.490† | 0.001 | | |
| TC/HDL-GCF TNF-$\alpha$ | | | 0.240* | 0.024 | | |
| GI-HDL | | | | | −0.352† | 0.007 |
| GI-LDL | | | | | 0.282* | 0.034 |
| GI-VLDL | | | | | 0.264* | 0.047 |
| BOP%- serum IL-6 | | | | | 0.290* | 0.028 |
| BOP%- GCF IL-6 | | | | | 0.405† | 0.001 |
| TC/HDL-serum IL-6 | | | | | 0.560† | 0.001 |
| TC/HDL-GCF IL-6 | | | | | 0.390* | 0.017 |

*$p < 0.05$.
†$p < 0.01$.
C, systemically healthy control group; HD, diet-suggested hyperlipidaemic group; HS, statin-prescribed hyperlipidaemic group, PI, plaque index; GI, gingival index; PPD, probing pocket depth; BOP%, percentage of bleeding on probing; CAL, clinical attachment level; GCF, gingival crevicular fluid; TC, total cholesterol; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; VLDL, very-low-density lipoprotein cholesterol; TRG, triglyceride TNF-$\alpha$, tumour necrosis factor-alpha; IL-1$\beta$, interleukin-1$\beta$, IL-6, interleukin-6; *r*, Pearson correlation coefficient.

Kim & Amar 2006). Cytokines such as IL-1$\beta$, IL-6 and TNF-$\alpha$ are produced locally within the diseased periodontal tissues and move into the periodontal pocket via GCF. Owing to its high vascularity, the periodontium may act as a potential source of systemic inflammatory mediators (Shub et al. 2006).

In this current study, there were significant positive correlations between serum and GCF IL-1$\beta$ and TNF-$\alpha$ levels and clinical periodontal parameters (especially PPD, CAL and BOP%) in mild or moderate hyperlipidaemic group (only diet suggested). Moreover, the present data showed that there were significant correlations between serum and GCF cytokines (IL-1$\beta$ and TNF-$\alpha$) and the TC/HDL ratio in the HD group. The results of the studies evaluating interactions between bacterial lipopolysaccharides and serum lipoproteins seemed to confirm these present results. The most commonly observed infection-induced lipid abnormalities in humans and experimental animals are increased TRG and VLDL levels (Cabana et al. 1989), and decreased HDL cholesterol levels (Kerttula et al. 1984). A decrease in total and LDL cholesterol levels has also been reported during severe bacterial infections (Akerlund et al. 1986). However, in rodents and rabbits, administration of lipopolysaccharide often leads to hypercholesterolemia (Cabana et al. 1989). Cytokines, such as TNF-$\alpha$ and IL-1$\beta$, induce a rapid increase in serum TRG, VLDL and cholesterol levels. Although the mechanism by which these cytokines increase the serum cholesterol levels is unknown, the increase in hepatic cholesterol synthesis may be due to an increase in the activity of 3-hydroxy-3-methyl glutaryl coenzyme A reductase (Feingold & Grunfeld 1987). The decreases in the activities of hepatic lipase and lipoprotein lipase may also be responsible for the infection-hyperlipidaemia relationship (Alvarez & Ramos 1986, Sammalkorpi et al. 1988).

According to the current findings, the HS group with periodontitis had higher serum and GCF IL-6 levels than both the systemically healthy control and the HD groups with periodontitis. Additionally, increased levels of BOP% were observed in the HSp group when compared with the HDp and Cp groups. Moreover, in the HS group, serum and GCF IL-6 levels were positively correlated with not only BOP%, but also the TC/HDL ratio. These present findings may confirm findings in the literature which demonstrate that IL-6 induces the production of acute phase proteins by the liver (Ramadori et al. 2010), and lead to an increase in hepatic fatty acid synthesis (Mendall et al. 1997). Although there are no another data reported regarding the periodontal status of hyperlipidaemic patients who are prescribed an anti-lipaemic agent, a previous study was performed to evaluate the effects of periodontal treatment on serum lipid levels in a hyperlipidaemic population prescribed a statin group anti-lipaemic drug (Fentoğlu et al. 2010). In that study, the positive effect observed on the lipids after periodontal treatment was described as stemming primarily from the treatment of gingivitis, representing active/acute inflammation. Previous findings (Fentoğlu et al. 2010) and the findings from the current study seem to support that, not only the degree of periodontal inflammation but also the deterioration in the lipid metabolism, may affect the bidirectional relationship between periodontal disease and hyperlipidaemia.

In conclusion, the present study suggests that the TC/HDL ratio manifested significant correlations with GI and BOP% in both hyperlipidaemic groups. While in severe cases of poor lipid metabolism, serum IL-6 became important, in mild or moderate cases of poor lipid metabolism, serum TNF-$\alpha$ and IL-1$\beta$ received attention. Periodontal disease is not only associated with the severity of the deterioration of lipid metabolism, but also that the worsening hyperlipidaemic state is associated with periodontal inflammation by increasing the serum and GCF pro-inflammatory cytokines. It is necessary to perform longitudinal evaluations in larger populations including patients with severe periodontitis in order to clarify the role of cytokines in the association between periodontal disease and hyperlipidaemia.

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**Clinical Relevance**

*Scientific rationale for the study*: Although there are several clinical studies on the association between periodontal health and serum lipids, there are currently no data clarifying the role of the potential mechanisms regarding the association between periodontal disease and hyperlipidaemia in terms of the pro-inflammatory cytokine cascade.

*Principal findings*: Serum and GCF levels of TNF-$\alpha$, IL-1$\beta$ and IL-6 seem to be related to the association of periodontal disease and hyperlipidaemia.

*Practical implications*: It is necessary to perform longitudinal evaluations in larger populations to clarify the role of pro-inflammatory cytokines in the mechanism of the association between periodontal disease and hyperlipidaemia.