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Effects of scaling and root planing and sub-antimicrobial dose doxycycline on oral and systemic biomarkers of disease in patients with both chronic periodontitis and coronary artery disease

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Abstract

Objectives: This study evaluated the effects of scaling and root planing (SRP) ± sub-antimicrobial dose doxycycline (SDD) on gingival crevicular fluid (GCF) levels of matrix metalloproteinase (MMP) -1, -8, -13 and on serum levels of high-sensitivity C-reactive protein (HsCRP) and lipid fractions in patients with *both* chronic periodontitis (CP) and coronary artery disease (CAD).

Material and Methods: Thirty-six patients were randomly distributed into two groups (Placebo or SDD; 6 weeks) and both received two regimens of SRP. At baseline and 6 weeks, GCF and blood were collected and clinical indices were recorded. MMPs, HsCRP and lipid fractions were assayed.

Results: There were statistically significant improvements for all clinical parameters, GCF volumes, GCF MMPs and serum levels of HsCRP, apolipoprotein-A (APO-A), high-density lipoprotein (HDL) and lipoprotein-a between pre- and post-treatment in both groups. Between groups, there were statistically significant greater improvements in pocket depth (PD), gingival index (GI), APO-A and HDL, favouring the group receiving SDD adjunctive to SRP ($p < 0.05$).

Conclusion: Greater improvement was detected for PD and GI, and for serum levels of APO-A and HDL cholesterol when using SRP+SDD compared with SRP+placebo in this study. An investigation with larger numbers of patients and a longer duration of drug treatment is needed to confirm these preliminary findings.

Key words: adjunctive treatment; cardiovascular disease; C-reactive protein; gingival crevicular fluid/analysis; host modulation therapy; matrix metalloproteinases; periodontitis/therapy; plasma lipids; subantimicrobial dose doxycycline

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Conflict of interest and source of funding statement

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The systemic implications of acute and chronic infections, such as chronic periodontitis (CP), have received considerable attention over the past decade (Smeeth et al. 2004, Moutsopoulos & Madianos 2006). Besides classical risk factors, such as hyperglycaemia, dyslipidaemia, hyperinsulinaemia, hypertension, diabetes and cigarette smoking, that may increase the probability of vascular atherogenic changes, chronic inflammatory diseases may also accelerate vascular inflammation and promote thrombosis (Craig et al. 2003, Iwamoto et al. 2003, Viles-Gonzalez et al. 2006, Croce & Libby 2007). Numerous cross-sectional studies have suggested that CP is a risk factor for atherosclerosis and subsequent cardiovascular disease (CVD) (Beck & Offenbacher 2005, D'Aiuto et al. 2005a, Yamazaki et al. 2005). However, whether an association between CP and CVD could be cause and effect is still uncertain.

There are a number of hypotheses to explain the association between CP and CVD. Periodontal pathogens, such as *Porphyromonas gingivalis*, and inflammatory mediators generated by the host's diseased periodontal tissues, such as the cytokines, interleukin 1β (IL-1β), tumour necrosis factor-α (TNF-α) and IL-6, may act directly, or indirectly, to exacerbate CVD (Mattilla et al. 2005). Bacteria from the subgingival biofilm may enter systemic circulation and colonize the coronary endothelium. The now dysfunctional endothelium could promote monocyte penetration into sub-endothelial tissues, adjacent to the shoulder of the atheroscleromatous plaque, where they differentiate into macrophages and foam cells that produce enzymes that cause cardiac events [i.e., acute myocardial infarction (AMI)]. Although periodontal pathogens have not been cultured from carotid or aortic atheromatous plaques, their presence has been inferred by positive polymerase chain reaction (PCR) assays (Haraszthy et al. 2000, Okuda et al. 2001) and more recently, Cavrini et al. (2005) have detected periodontal pathogens in atheromatous plaques by fluorescence in situ hybridization. Another possibility for the contribution of CP to CVD is that cytokines synthesized locally, in inflamed periodontal tissues, can be carried by the circulation to the liver where they induce the expression of acute phase proteins including (but not limited to) C-reactive protein (CRP), fibrinogen and haptoglobin. CRP can then form a complex with enzyme- or oxidant-modified low-density lipoprotein (LDL) cholesterol, which, when phagocytosed by infiltrating monocytes, induces their differentiation into macrophages and foam cells (Østerud & Bjørklid 2003). The production of matrix metalloproteinases (MMPs), such as MMP-8 (collagenase-2) and MMP-9 (gelatinase B) by these inflammatory cells, can degrade the thin collagen ''cap'' that covers cholesterol-rich plaques lining the coronary arteries causing plaque rupture, resulting in thrombosis and AMI (Falk et al. 1995, Libby 1995, Lee & Libby 1997). An elevated serum level of high-sensitivity CRP (HsCRP) is a biomarker of systemic inflammation and significantly increases the risk for CVD in combination with other risk profile factors (Persson et al. 2005). Recently, studies have shown that severe CP may also induce elevated serum CRP levels (Noack et al. 2001, Craig et al. 2003, D'Aiuto et al. 2004b). Moreover, some studies (but not all) have shown that periodontal treatment can reduce the serum levels of these biomarkers of systemic inflammation such as CRP (Mattilla et al. 2002, Iwamoto et al. 2003, D'Aiuto et al. 2004a, 2005b). In this regard, a recent study revealed a ''spike'' of acute phase proteins in the circulation of patients with severe CP soon after a vigorous regimen of SRP. However, this increase in systemic inflammatory markers was short-lived and was followed by a reduction of these biomarkers, compared with baseline values, over the long term (Tonetti et al. 2007).

It is well established that acute and chronic infections influence lipoprotein levels as a part of the acute phase reaction in a way that may favour atherogenesis and CVD (Khovidhunkit et al. 2000, Mattilla et al. 2005). Several pathogens that cause chronic infection may induce alterations in lipoprotein metabolism. These pathogens include *Chlamydia pneumoniae* (Laurila et al. 1997), *Helicobacter pylori* (Laurila et al. 1999) and periodontal pathogens (Lösche et al. 2000). Thus, recently, increased attention has been paid to the effect of periodontitis on both lipoproteins and inflammatory markers systemically in the circulation, two major contributors to the pathogenesis of CVD.

MMPs are tissue destructive, host-derived, calcium and zinc-dependent neutral proteinases that are not only involved in numerous pathologic conditions, including cardiovascular and periodontal diseases, but also in physiologic tissue remodelling associated with organogenesis, growth and normal tissue turnover (Kiili et al. 2002, Sorsa et al. 2004). MMP-1 is distributed widely in tissues and expressed by fibroblasts, keratinocytes, endothelial cells, osteoblasts, chondrocytes and macrophages. MMP-1 is an important regulator of connective tissue and is present in inflamed gingival regions, including periodontal disease (Tüter et al. 2002). Although initially identified as a fibroblast-type collagenase, which can degrade the triple-helical collagen molecule, MMP-1 is now known to degrade a wide range of other substrates, including various structural extracellular matrix (ECM) components as well as soluble non-matrix mediators and other MMPs. MMP-8, initially called leucocyte-type collagenase, like MMP-1, also has wide substrate specificity and is the major type of collagenase detected in the gingival tissue, gingival crevicular fluid (GCF) and saliva of humans with periodontitis (Kiili et al. 2002, Kinane et al. 2003). In fact, Golub et al. (1997) found that the relative proportion of the three genetically distinct types of collagenase in the GCF of patients with CP was 96% MMP-8, 4–5% MMP-13 and $<1\%$ MMP-1. MMP-8 is now known to be produced not only by polymorphonuclear leucocytes but also by resident synovial and gingival fibroblasts, epithelial cells, odontoblasts, plasma cells, oral cancer cells and monocyte/macrophages (Sorsa et al. 2004). The third member of the collagenase subfamily, MMP-13, is expressed during bone development as well as in gingival–oral and foetal wound healing (Kiili et al. 2002) and has been detected in human gingival sulcular epithelium in patients with CP and in gingival fibroblasts (Mancini et al. 1999, Tervahartiala et al. 2000).

ECM degradation, during various periodontal diseases, is mediated by a complex cascade involving both host- and microbial-derived proteinases (Golub et al. 1991). The importance of the host inflammatory response in periodontal pathogenesis presents an opportunity to exploit new treatment strategies for periodontitis by means of host response modulation (Golub et al. 1992). Host modulatory therapy can be combined with traditional periodontal

therapies that reduce the bacterial burden. Sub-antimicrobial dose doxycycline (SDD) marketed as Periostat® is the only Food and Drug Administration-approved, systemic therapy for the treatment of periodontal diseases adjunctive to scaling and root planing (SRP). It was developed to treat the host inflammatory response in periodontal pathogenesis and functions by inhibiting the activity and/or down-regulating the expression of MMP's, such as collagenase and gelatinase, and cytokines, such as IL-1β and TNF-α, and other mediators of inflammation and connective tissue destruction including excessive bone resorption (Golub et al. 1991, 1992, Lee et al. 2004).

Brown et al. (2004) recently showed that patients with acute coronary syndromes, which included a history of CVD, atherosclerosis in coronary arteries and unstable angina, who were treated for 6 months with SDD in a double-blind study, showed dramatic, and statistically significant, reductions in plasma markers of systemic inflammation and ECM degradation including HsCRP, IL-6 and MMP-9. Placebo-treated patients showed no significant changes in any of these parameters. However, periodontal disease was *not* treated or assessed in that study.

The aim of the present study was to evaluate the effects of phase I periodontal therapy, consisting of SRP, with or without SDD, on clinical parameters, GCF levels of MMP-1, -8, -13 and also on the serum levels of HsCRP and lipid fractions in patients who exhibited *both* CP and CAD. To our knowledge, this is the first study to determine the effect of SRP $\pm$ SDD in patients with *both* CP and coronary artery disease (CAD).

Material and Methods

Study population and study design

Informed consent

The protocol of this randomized, double-blind clinical trial was approved by both the Ethical Committees of the Faculty of Medicine and the Faculty of Dentistry, Gazi University, Ankara, Türkiye. Informed written consent was obtained from all subjects after the details of the clinical procedures, including periodontal measurements, blood and GCF sampling, and the host modulatory drug were fully explained. Before consent, information on the safety and potential efficacy of SDD, and the probability of receiving SDD or placebo, was also explained. Subjects were recruited from patients referred to the Department of Cardiology of Gazi University. A total of 36 patients were enrolled into the study.

Inclusion/exclusion criteria

Patients referred to the Department of Cardiology of Gazi University who had angiographically proven CAD, defined as the presence of a $\geqslant$50% lesion in any major coronary artery or left main stem, were screened for inclusion in the study. Exclusion criteria included diabetes mellitus, current smoking, unstable CAD, congestive heart failure or markedly impaired left ventricular dysfunction [ejection fraction (EF) $<$40%], a coronary angiography performed within the last 4 weeks and an age >70 years. Potential subjects were then screened for periodontal disease status at the Department of Periodontology of Gazi University. Periodontal disease status was determined according to clinical and radiographic criteria. Patients showing radiographic evidence of bone loss and attachment loss and those who had a minimum of six periodontal pockets >4 mm were included in the study. None of the patients had received periodontal treatment during the past 6 months and none had received antibiotic medication during the past 3 months. The clinical evaluation of patients was based on the following indices: plaque index (PI) (Silness & Löe 1964), gingival index (GI) (Löe 1967), probing depths (PD) and clinical attachment loss (CAL).

Medical history

All 36 subjects were on statin therapy and none of them used anti-aggregant therapy other than salicylates. The subject's cardiac medical therapy and diet habits did not change during the study. Subjects and their medical records were reviewed for a family history of CAD. A positive family history of CAD was defined as a documented myocardial infarction, angiographic evidence of CAD, angina pectoris or sudden cardiac death in a first- or second-degree relative who was a male, 55 years or younger or was a female 65 years or younger. Subjects were considered to have hypertension if they had been prescribed medications to lower blood pressure or had blood pressure values of $\geqslant$140/90 mmHg on two or more occasions.

Clinical procedures

All clinical parameters were measured with a Goldman/Fox Williams probe calibrated in millimetres. All single-rooted teeth present in the subject, in both the upper and lower sextants, were used as test sites for PD and CAL measurements and for GCF sampling. Clinical measurements were taken at six sites per tooth (mesio-buccal, mid-buccal, disto-buccal, mesio-palatal, mid-palatal and disto-palatal) from the test sites. The deepest six pockets found in the test site (single-rooted teeth) of each subject were chosen for GCF sampling. Therefore, 216 (36 patients $\times$ six sites) pockets were sampled for GCF at each of the test appointments.

The 36 patients were randomly assigned to either group I or II, using a completely randomized design, by the corresponding author who did not provide any patient treatment or participate in any clinical measurements or laboratory analysis. No other participant in the study had access to the blinded information, including the statistician, until all the data had been collected and analysed. All subjects received SRP. In addition to SRP, group I patients were placed on placebo and group II patients were placed on SDD therapy (20 mg Periostat® bid; Drug and identical-appearing placebo were provided by Alliance Pharmaceuticals Ltd., Wilshire, UK) for 6 weeks. Blood and GCF were sampled and clinical index scores were recorded, at baseline. After the baseline clinical recording and blood and GCF sampling, phase I periodontal therapy was initiated for both groups and SRP was accompanied by SDD therapy for group II, whereas placebo and SRP were administered to patients in group I. All patients underwent phase I therapy, including oral hygiene instruction, and SRP under local anaesthesia. Full-mouth SRP was performed once a week for 2 weeks by sharp sickles, gracey and universal curettes and ultrasonic instruments.

After 6 weeks, clinical measurements were again obtained and blood and GCF were collected, and the subjects were questioned about drug compliance and any possible adverse reactions.

Blood sampling and laboratory analyses

At the baseline and 6-week appointments, a fasting (12 h) blood draw was taken before conducting the dental

procedures. The blood was processed to isolate serum and plasma and then the serum or plasma was analysed immediately. Total cholesterol, high-density lipoprotein (HDL) cholesterol and triglyceride levels were measured in the serum by enzymatic assays using an Aeroset autoanalyser (Abbott Laboratories, Chicago, IL, USA). LDL cholesterol was calculated using Friedewald's formula: LDL cholesterol = total cholesterol − [HDL cholesterol + (triglycerides/5)]. Hs-CRP, apolipoprotein A (APO-A), apolipoprotein B (APO-B) and lipoprotein a (Lp a) levels were assayed in the plasma on a Behring BN-ProSpec Nephelometer (Dade Behring, Marburg, Germany).

GCF sampling and processing

GCF samples were collected using commercially available periopaper (Oraflow Inc., Plainview, NY). The sample site was gently air-dried and all supragingival plaque was removed. The area was carefully isolated with cotton rolls and a saliva ejector was used to prevent the samples from being contaminated by saliva. The paper strips were inserted into the pockets until slight resistance was felt and left in place for 30 s. Care was taken to avoid mechanical injury of the gingival tissues. Strips contaminated by bleeding or exudate were discarded. Strips were placed into coded sealed plastic microcentrifuge tubes and covered with paraffin and then stored at -70°C until processed. GCF volumes were determined as described previously (Tüter et al. 2002). GCF collection always preceded pocket depth probing to avoid mechanical stimulation of GCF flow.

GCF enzyme-linked immunoabsorbent assay (ELISA) analysis for MMP-1, -8 and -13

The levels of MMP-1, -8 and -13 in GCF samples were assayed using a sandwich ELISA (Quantikine R&D Systems Inc., Minneapolis, MN, USA). All ELISA procedures were carried out according to the manufacturer's instructions. Microcentrifuge tubes, containing a PerioPaper strip, with absorbed GCF sample, were removed from storage and warmed to 4°C, and then eluted using a centrifugal method (Griffiths et al. 1988). Elution was carried out by adding 200 μl of calibrator diluent (MMP-1 and MMP-13) or 100 μl of diluent (MMP-8) to the strip and then the microcentrifuge tubes, containing the strips and the buffer, were centrifuged for 20 min. at 3000 *g*. After centrifugation, the strips were removed and the fluid was assayed by ELISA for MMP-1, -8 and -13. The ELISA plates were then assessed spectrophotometrically at optical density (OD) at 450 nm with a reference filter of OD at 540 nm. The levels of GCF MMP-1, -8 and -13 in each sample were determined using the concentration values of the standards included with the kit. Total collagenase was determined by the arithmetic summation of MMP-1, -8 and -13 totals.

Statistical analysis

Data analysis was performed using the statistical package SPSS (Microsoft Corp., Chicago, IL, USA). The Shapiro–Wilks test was used to determine the normality of the data's distribution. The statistical significance of the differences in GCF levels of MMP-1, -8 and -13, serum levels of lipid fractions and HsCRP and clinical parameters between pre- and post-treatment were analysed using the Wilcoxon Signed Rank test. Mann–Whitney *U*-tests were used to determine the significance of the differences between the two groups at baseline and post-treatment for all parameters. The χ^2-test was used to determine whether there was a statistical difference between the groups with respect to age, hypertension, gender and a family history of CAD. We could not prospectively calculate the power needed in this study from the literature because the literature did not contain any studies that examined the effects of SRP *and* LDD on subjects that were diagnosed with *both* periodontitis *and* coronary artery disease. Using the data that were generated with our study, we retrospectively calculated the power [$(1-\beta)$ calculation] to observe a statistically significant difference in PD, between the two groups, to be 82.96%. A p-value <0.05 was considered to be statistically significant for all statistical tests.

Results

No adverse events occurred during this preliminary clinical trial and none of the subjects asked to be withdrawn from the study or stopped taking their assigned study drug. There were no significant differences between the two groups with respect to age, gender, hypertension or family history (Table 1). Table 2 compares the four clinical parameters (PI, GI, PD and CAL) and the GCF volumes, pre- and post-treatment, within each group and also compares these parameters, pre- and post-treatment, between the two groups. At the pre-treatment time point, there were no significant differences between groups I and II for the clinical parameters or for GCF volumes. At the post-treatment time point, there were no significant differences between groups I and II for PI, CAL or GCF volumes but group II showed statistically significant decreases in GI and PD in comparison with group I; $p = 0.027$ and 0.034, respectively. Within each group, all the clinical parameters and the GCF volumes showed statistically significant reductions at the post-treatment time point.

Figure 1 presents the data for the levels of MMP-1, -8 and -13 and total collagenase, pre- and post-treatment, for groups I and II. Within groups I and II, there were statistically significant reductions in all MMPs and total collagenase at the post-treatment time point compared with pre-treatment values. At both the pre- and post-treatment time points, there were no statistically significant differences between the two groups for MMPs or total collagenase.

The serum HsCRP levels for the two groups, pre- and post-treatment, are shown in Fig. 2. There was no significant difference in the HsCRP levels between groups I and II pre-treatment ($p = 0.864$). The serum levels of HsCRP

Table 1. Comparison of the general characteristics of subjects in each group

	Group I (placebo) ($n = 18$)	Group II (SDD) ($n = 18$)	p
Average age (years)	52.2 ± 6.91	55.39 ± 9.38	0.293
Gender (male/female)	17/1	16/2	0.5
Family history of CAD (±)	8/10	9/9	0.738
History of hypertension (±)	13/5	13/5	1.000

CAD, coronary artery disease; SDD, sub-antimicrobial dose doxycycline.

Table 2. Comparison of clinical parameters and GCF volumes for groups I and II, pre- and post-treatment, and comparison of clinical parameters and GCF volumes, pre- and post-treatment, between groups I and II

	Group I (placebo) ($n = 18$) Median (quarters)			Group II (SDD) ($n = 18$) Median (quarters)			p^*	
	pre-treatment	post-treatment	$p^\dagger$	pre-treatment	post-treatment	$p^\dagger$	pre-treatment	post-treatment
Plaque index	2.0 (1.75–2.16)‡	0.75 (0.23–0.92)	<0.001	2.0 (1.5–2.21)	0.55 (0.17–1.0)	<0.001	0.673	0.696
Gingival index	1.90 (1.83–2.08)	1.27 (0.97–1.52)	0.001	1.99 (1.86–2.21)	1.0 (0.77–1.16)	<0.001	0.214	0.027
Pocket depth (mm)	4.59 (4.18–4.72)	3.78 (3.52–4.2)	0.001	4.44 (4.19–4.8)	3.45 (3.24–3.69)	<0.001	0.839	0.034
Clinical attachment loss	4.26 (3.95–4.72)	4.0 (3.66–4.46)	0.001	4.08 (4.0–4.39)	3.97 (3.75–4.10)	<0.001	0.673	0.521
GCF volume (μl)	2.53 (2.17–3.2)	1.95 (1.68–2.21)	<0.001	2.37 (1.95–2.76)	1.85 (1.41–2.28)	0.001	0.226	0.323

*Comparison between groups (Mann–Whitney *U*-test).
†Change between pre- and post-treatment within a group (Wilcoxon's signed-rank test).
‡The numbers in parentheses are the 25th and 75th percentiles of the raw data.
GCF, gingival crevicular fluid; SDD, sub-antimicrobial dose doxycycline.

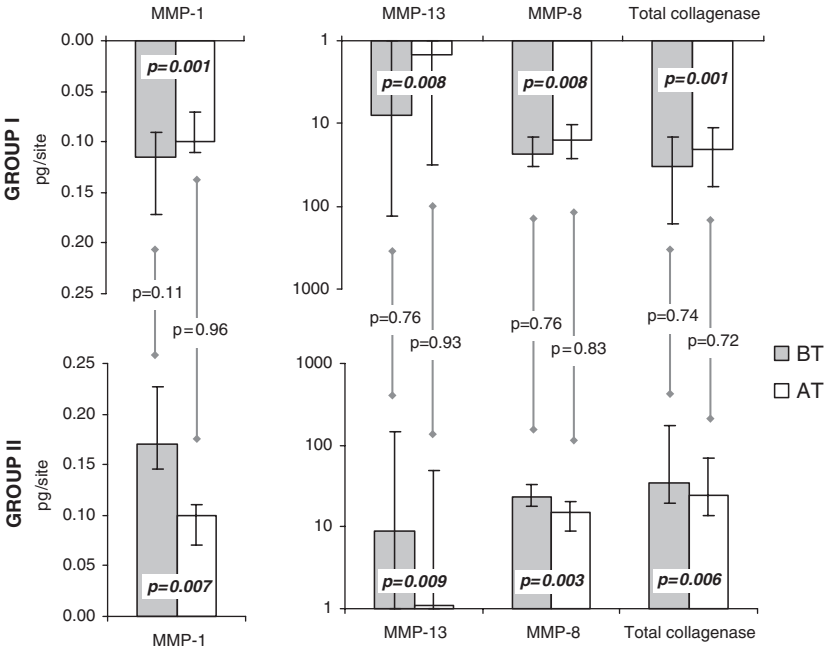

Fig. 1. Gingival crevicular fluid levels of matrix metalloproteinase (MMP)-1, -8 -13 and total collagenase in groups I and II before and after treatment and also a comparison of enzyme levels between the two groups both before and after treatment.

were significantly decreased within both groups ($p < 0.001$). There was no statistically significant difference for the HsCRP levels between the two groups post-treatment ($p = 0.628$). The alteration of HsCRP levels between the two groups showed no significant difference post-treatment ($p = 0.791$). Ejection fractions were not different between the two groups both at baseline ($p = 0.988$) and 6 weeks ($p = 0.117$) (data not shown).

The blood lipid and lipoprotein levels of the two groups pre- and post-treatment are shown in Table 3. There was no significant difference in blood lipid and lipoprotein levels between groups I and II pre-treatment. After treatment, HDL cholesterol and APO-A levels increased and Lp(a) levels decreased significantly in both groups. However, there were significantly greater increases in both HDL cholesterol and APO-A, the protein core of HDL, post-treatment in group II than in group I ($p = 0.047$ and $p = 0.006$, respectively).

Discussion

Chronic destructive periodontal disease is increasingly being recognized not only as a localized inflammatory disease (albeit the major cause of tooth loss in the adult population world wide) but also as a most common condition with an impact on a variety of medical diseases as well. In this regard, CP can be a risk factor for CVD, stroke, bacterial pneumonia and less well-regulated diabetes mellitus (Ryan 2006). Thus, the question has been asked: can periodontal therapy that effectively reduces local inflammation reduce the risk for CVD? In this regard, several studies have found that periodontal therapy, i.e., SRP, can reduce the level of circulating biomarkers of systemic inflammation. For example, periodontal therapy was found to reduce significantly plasma levels of CRP after 6 weeks (Mattilla et al. 2002) and after 6 months (D'Aiuto et al. 2004a, b). However, studies by other groups (Ide et al. 2003, Yamazaki et al. 2005) did not observe significant changes in these systemic biomarkers after periodontal therapy consisting of SRP. D'Aiuto et al. (2006) studied the effect of SRP or intensive periodontal treatment (IPT; SRP+locally applied minocycline) in patients with severe generalized periodontitis but otherwise in good health. They found that patients receiving IPT showed significant decreases in CRP, IL-6, total cholesterol and LDL cholesterol in comparison with patients in the SRP group. In a subsequent study, an early ''spike'' (i.e., a sharp increase) in the biomarkers of systemic inflammation (e.g., CRP) due to SRP was seen, but this was followed later by a reduction in these biomarkers compared with the pre-treatment values (Tonetti et al. 2007). It should be noted, however, that the effect of local therapy on systemic biomarkers in these studies was not assessed in patients who had

been diagnosed with CVD but in otherwise healthy patients. In contrast, Brown et al. (2004) carried out a double-blind placebo-controlled study on CVD patients administered a 6-month regimen of a non-antimicrobial formulation of doxycycline (i.e., low-dose doxycycline-SDD) approved as an MMP-inhibitor drug for the management of CP. They found a 40–50%, statistically significant reduction in circulating (i.e., plasma) levels of HsCRP, IL-6 and MMP-9, all of which are recognized as being important risk factors for CVD and cardiac events (Ridker 2001, Blankenberg et al. 2003). However, the effect of SDD on the periodontal condition of these CVD patients was *not* assessed. As a result, it was unclear whether these beneficial changes in systemic biomarkers, produced by this dental medication, produced these effects either directly, by direct inhibition of cytokine expression and MMP activity in the diseased coronary arteries, or indirectly by first reducing the production of inflammatory mediator molecules in the diseased periodontal tissues in the CVD patient, which, subsequently, reduced acute phase proteins produced by the liver and their risk for cardiac events. Another difference between the Brown et al. (2004) study and this study is that patients with unstable CAD were excluded in this study whereas they were included in the Brown et al. (2004) study. In this current preliminary short-term (6-week) study, we began to address these issues in CVD patients by determining the effect of either a repeated regimen of SRP alone or SRP combined with systemic administration of SDD as a host-modulatory agent. Although the serum HsCRP levels were significantly decreased after the therapies in both the groups, there was no significant difference between the two groups at 6 weeks in our study. The lack of additional benefit of SRP+SDD (combination therapy) *versus* SRP alone on this biomarker of systemic inflammation may reflect (1) the short-term duration of SDD in this study (6 weeks) in contrast to the previous study by Brown et al. (2004) in which SDD was administered (without SRP) for 6 months and (2) the ability of SRP alone in this study to reduce elevated HsCRP to low levels, at least in the short term. However, it is conceivable that 6 months after SRP, SDD would be required to maintain this beneficial effect after the efficacy of SRP has worn off and the bacterial ''burden'' in the periodontal pockets has been re-established.

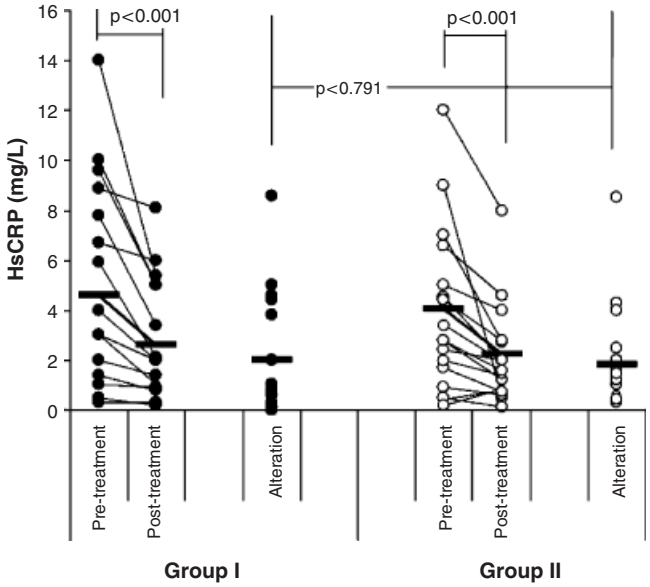

Fig. 2. Serum levels of high-sensitivity C-reactive protein (HsCRP) for the two groups before and after treatment and the alteration of HsCRP levels after the therapies. Horizontal bars represent the sample means.

The combination of SDD and SRP has repeatedly been shown to reduce collagenase, gelatinase and serpinolytic (α1-proteinase inhibitor degrading) activity in GCF and gingiva in patients with CP more than SRP alone (Golub et al. 1990, Crout et al. 1996, Preshaw et al. 2004). In one such study, the combination of SDD and subgingival scaling reduced pyridinoline cross-

Table 3. Blood lipid and lipoprotein levels in both groups before and after treatment and comparison between the two groups

	Group I (placebo) (n = 18) Median (quarters)			Group II (SDD) (n = 18) Median (quarters)			p*	
	pre-treatment	post-treatment	p†	pre-treatment	post-treatment	p†	pre-treatment	post-treatment
Total cholesterol (mg/dl)	153.5 (137.2–165.0)‡	151.0 (126.0–159.0)	0.337	163.5 (152.7–177.7)	156.0 (153.5–181.5)	0.492	0.068	0.068
LDL cholesterol (mg/dl)	85.1 (77.6–105.3)	77.1 (67.3–95.1)	0.084	91.6 (79.5–105.8)	84.8 (77.1–95.9)	0.338	0.389	0.406
HDL cholesterol (mg/dl)	38.0 (32.0–42.0)	38.0 (35.0–46.0)	0.024	40.5 (38.5–43.2)	44.0 (39.7–50.5)	0.003	0.161	0.047
VLDL cholesterol (mg/dl)	25.4 (17.7–35.0)	24.5 (21.2–32.8)	0.306	29.8 (18.2–43.5)	22.0 (17.3–45.8)	0.862	0.355	0.864
Triglyceride (mg/dl)	127.0 (88.7–175.2)	122.5 (106.0–164.2)	0.306	149.0 (91.0–217.5)	110.0 (86.7–229.0)	0.862	0.355	0.864
Lipoprotein-a (mg/dl)	42.0 (15–51.2)	14.0 (9.7–38.5)	0.003	25.5 (11.5–39.5)	11.0 (9.0–17.0)	0.002	0.323	0.406
Apolipoprotein-A (mg/dl)	102.5 (98.0–117.7)	110.0 (103.7–134.0)	0.033	119.0 (104.7–133.2)	128.5 (116.2–140.7)	0.031	0.064	0.006
Apolipoprotein-B (mg/dl)	78.0 (60.0–95.5)	85.0 (68.5–103.2)	0.102	94.0 (80.0–108.0)	87.5 (76.0–98.0)	0.183	0.068	0.673

*Comparison between groups (Mann–Whitney U-test).

†Change between pre- and post-treatment within a group (Wilcoxon's signed-rank test).

‡The numbers in parentheses are the 25th and 75th percentiles of the raw data.

SDD, sub-antimicrobial dose doxycycline; LDL, low-density lipoprotein; HDL, high-density lipoprotein; VLDL, very low-density lipoprotein.

linked carboxyterminal telopeptide of type I collagen (ICTP) levels, in addition to collagenase, in periodontal pockets, whereas scaling alone had no effect (Golub et al. 1997). ICTP is a degradation product of type I collagen used to assess bone resorption, when measured in blood or urine, in patients with bone deficiency diseases such as osteoporosis and has been monitored in the GCF of periodontal pockets to assess bone resorption at these local sites in both humans and experimental animals (Giannobile et al. 1995). However, the current study is the first to assess the combination of SDD and SRP in the treatment of patients with *both* CP and CAD. Although all the GCF levels of MMPs decreased significantly after the therapies in both groups, there was no significant difference between two groups post-treatment in the present study. In contrast to these previous studies, we prescribed SDD for a shorter time (6 weeks). In fact, SDD administration for just 2 or 3 weeks inhibited collagenase activity in the gingival tissues and GCF collected from CP patients (Golub et al. 1990, Lee et al. 2004). However, it should be recognized that in the earlier studies, SDD reduced collagenase and gelatinase enzyme activities, whereas enzyme activity was *not* measured in the current study; only the protein levels of these enzymes were determined. It is not known what proportion of MMPs measured in this study were in active or inactive (proMMPs) forms.

Regarding clinical measures of periodontal disease severity in these CAD patients, although all the clinical parameters were significantly improved after the therapies in both groups, SDD in combination with SRP provided a better clinical improvement beyond that obtained by SRP alone in the present study. In particular, PD and GI scores showed a significantly greater reduction, in the combination therapy group, than SRP alone post-treatment. Once again, the clinical significance of this effect of non-surgical periodontal therapy in CAD patients remains to be clarified by larger studies of longer duration.

In the present study, the lipid fractions were not statistically different between the two groups pre-treatment. After the therapies, APO-A and HDL cholesterol levels significantly increased and Lp(a) levels significantly decreased in both groups. Of particular interest, the combination of SRP+SDD did significantly increase the levels of HDL cholesterol, and its core protein APO-A lipoprotein, more than SRP alone, indicating, based on these blood lipid fractions, that SDD+SRP therapy conceivably could reduce the risk for CVD, including coronary events such as AMI. But additional studies with larger numbers of patients and for longer time periods will be needed to confirm these findings. The levels of HDL cholesterol and APO-A are decreased during acute and chronic inflammatory conditions (Lippi et al. 1998, Schlitt et al. 2005) and HDL can bind and neutralize endotoxin (lipopolysaccharide) that is directly involved in mediating the inflammatory process (Baumberger et al. 1991). HDL can also inhibit the formation of foam cells by promoting cholesterol efflux from monocytes/macrophages (Schlitt et al. 2005). In addition to its other anti-atherothrombotic functions, HDL can inhibit cytokine-induced expression of adhesion molecules such as vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) by endothelial cells (Barter 1997). These effects could explain, at least in part, the influence of inflammatory periodontal disease on CVD and the greater ability of the ''two-pronged'' treatment, i.e., bacterial ''load'' reduction by SRP combined with host-modulation therapy with SDD, to reduce more effectively the severity of CP and the risk for cardiac events. We hypothesize that the increasing amounts of HDL cholesterol and APO-A in both groups are important because it has been reported that every 1 mg/dl increase in HDL cholesterol is associated with a 2–3% decrease in CAD risk, independent of LDL cholesterol and triglyceride levels (Castelli et al. 1986). It has also been reported that HDL cholesterol could be a therapeutic target due to this protective effect (Toth 2005). In fact, based on the Framingham study (Castelli et al. 1986), the combination of SRP plus SDD, by increasing HDL cholesterol twice as much as SRP alone, could reduce the risk for CVD proportionately.

To our knowledge, the current study is the first to demonstrate the effects of SRP ± SDD on both periodontitis and systemic biomarkers of inflammation in CVD patients. In view of our results, combination therapy produced statistically significant benefits in both local periodontal disease (GI and PD) and systemic biomarkers (HDL cholesterol and APO-A). However, it is not yet clear whether SDD reduces risk for cardiac events, after combination therapy, and whether these effects are due to direct effects on CAD or indirect effects resulting from improved periodontal health. Further investigations with larger numbers of subjects and of a longer duration are needed to better understand the role of periodontal therapy with/without adjunctive SDD in patients with *both* CP and CAD.

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Clinical Relevance

Scientific rationale for the study: CP may contribute to systemic inflammation that increases the risk of CAD, and reduction of local inflammation by aggressive treatment of CP may reduce systemic inflammation as well.

Principal findings: SRP ± SDD in patients with both CP and CAD both resulted in improved clinical parameters and GCF levels of MMP-1, -8 and -13. Serum levels of HsCRP and Lp(a) decreased, whereas APO-A and HDL levels increased in both groups. However, SRP+SDD resulted in significantly greater improvements in PD, GI, APO-A and HDL levels compared with SRP+placebo.

Practical implications: Treating CP with SRP or SRP+SDD reduces both local and systemic inflammation; however, SRP+SDD had greater efficacy on some local and systemic outcomes.