Periodontal infections cause changes in traditional and novel cardiovascular risk factors: Results from a randomized controlled clinical trial

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Background Chronic infections, such as periodontitis, are associated with increased risk of systemic diseases driven by a persistent low-grade systemic inflammation and metabolic changes. Severity of periodontitis has also been associated with increased systolic blood pressure (BP). However, the issue remains poorly investigated. We aimed to estimate the effect of periodontal therapy on traditional and novel cardiovascular risk factors in systemically healthy individuals who have periodontitis.

Methods We enrolled 40 otherwise healthy patients with severe chronic generalized periodontitis in a 6-month pilot intervention trial. Individuals were randomized either to a standard course of periodontal therapy (subgingival scaling and root planing) or an intensive one (including the adjunctive use of a locally delivered antimicrobial, IPT).

Results Compared to control, IPT produced significant reductions in a cluster of inflammatory markers at 1 ($P = .0406$) and 2 ($P = .0060$) months together with an improvement in lipid markers at 2 ($P = .0320$) and 6 ($P = .0432$) months after therapy. Intensive periodontal therapy produced greater reductions in IL-6 at 1 (0.4 ± 0.2 ng/L difference, 95% CI 0.03-0.9, $P = .0284$) and 2 months (0.3 ± 0.2 ng/L difference, 95% CI 0.1-0.8, $P = .0284$), together with decreases in C reactive protein (0.4 ± 0.2 mg/L difference, 95% CI 0.01-0.8, $P = .0438$) and total cholesterol (0.3 ± 0.1 mmol/L difference, 95% CI 0.04-0.6, $P = .0254$). Moreover, a 7 ± 3-mm Hg decrease in systolic BP was observed at 2 months in the IPT group (95% CI 1-12, $P = .0211$), and this difference was greater in current smokers (14 ± 5 mm Hg 95% CI 3-25, $P = 0.0124$). Intensive periodontal therapy subjects exhibited a $1.53\% \pm 1.20\%$ (95% CI 1.05-2.24, $P = .0290$) and $2.00\% \pm 1.42\%$ (95% CI 0.98-4.09, $P = .0568$) decreases in cardiovascular risk scores (Framingham) at 2 and 6 months, respectively, when compared to those in the standard group.

Conclusions Our findings suggest that intensive periodontal treatment reduces systemic inflammatory markers and systolic BP, and improves lipid profiles with subsequent changes in cardiovascular risk when compared to standard therapy. (Am Heart J 2006;151:977-84.)

Periodontal infections are commonly thought to have limited influence on general health. Since the beginning of the last century, however, physicians hypothesized a potential pathological effect of oral infections on the onset and progression of serious systemic diseases.[1] Epidemiological evidence produced mostly in the last decade suggests the existence of a plausible biological association between oral health and a series of systemic illnesses (preeclampsia, coronary atherosclerotic events, cerebrovascular ischemia, respiratory infections, and metabolic syndrome).[2-5] A recent systematic review in particular indicated that periodontitis is associated with a moderate risk of future cardiovascular events in otherwise healthy individuals.[6,7] For individual patients, the chronic infectious–inflammatory burden of periodontitis may represent a possible contributor to other systemic inflammatory diseases (eg, metabolic syndrome and atherosclerosis). Oral infections as triggers of a state of chronic systemic inflammation represent one mechanistic explanation.

However, this issue remains poorly investigated. It is likely that other important factors (smoking, sex, body

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Table I. Baseline patient characteristics

Variable	Overall (N = 40)	SPT (N = 20)	IPT (N = 20)	*P**
Age, y	48 ± 7 (46-51)	47 ± 7 (45-52)	48 ± 7 (45-52)	.8281
Sex, male	22	10	12	.7512†
Ethnicity, white	30	13	17	.1981†
BMI, kg/m^2	26 ± 4 (24-27)	25 ± 4 (24-28)	26 ± 4 (24-28)	.9675
Systolic BP, mm Hg	134 ± 15 (129-139)	131 ± 16 (125-140)	135 ± 14 (129-143)	.4329
Diastolic BP, mm Hg	86 ± 10 (83-89)	85 ± 11 (81-91)	86 ± 11 (82-91)	.8533
Never smokers	30	15	15	1.0000†
Current and former	10	5	5	
Family history of CVD	26	11	15	.3202†
IL-6, ng/L‡	1.4 ± 0.9 (1.4-1.9)	1.5 ± 1.0 (1.4-2.3)	1.3 ± 0.9 (1.1-1.9)	.2333
CRP, mg/L‡	2.0 ± 1.8 (1.9-3.0)	2.2 ± 2.2 (1.8-3.9)	1.8 ± 1.1 (1.6-2.7)	.2074
WBC, 10^9/L‡	6.9 ± 1.9 (6.6-7.8)	6.6 ± 1.6 (6.0-7.5)	7.3 ± 2.2 (6.6-8.6)	.2065
Cholesterol, mg/dL‡	209 ± 27 (201-221)	209 ± 23 (197-221)	209 ± 27 (197-224)	.7252
HDL-C, mg/dL‡	50 ± 16 (50-58)	50 ± 16 (46-62)	54 ± 16 (46-62)	.6108
Triglycerides, mg/dL‡	133 ± 98 (106-160)	142 ± 98 (98-186)	124 ± 98 (80-168)	.5164
LDL-C, mg/dL‡	128 ± 23 (124-136)	128 ± 23 (116-139)	132 ± 23 (120-143)	.5787

* Independent *t* test comparing IPT subjects with controls.
† χ^2 test for dichotomous variables comparing IPT subjects with controls.
‡ Geometric mean values are reported.

mass index [BMI], age, and socioeconomic status) that are associated with both periodontitis and cardiovascular disease risk act as confounders on this association. Preliminary evidence from this group has raised the hypothesis that periodontal infections might influence systemic health through an increased systemic inflammatory state.[8] Untreated periodontitis and its clinical manifestations (tooth loss) have also been associated with increased systolic blood pressure (BP) in subjects with essential hypertension[9] and in postmenopausal women.[10]

To further address this matter, we conducted a pilot randomized single-blind intervention trial comparing the effects of intensive (IPT) versus control standard periodontal therapy (SPT) on markers of inflammation, serum lipids, and BP.

Methods

Following protocol review and approval by the University College London Hospitals ethics committee, enrolment included individuals referred to the Eastman Dental Hospital for treatment of severe generalized periodontitis. Individuals having at least 50% of their dentition with periodontal probing pocket depths >4 mm and with documented radiographic alveolar bone loss were included. Subjects with (1) known systemic diseases; (2) history and/or presence of other infections; (3) systemic antibiotic treatment in the preceding 3 months; (4) treatment with any medication known to affect the serum level of inflammatory markers, lipids, or BP; (5) pregnant or lactating females; (6) allergy to tetracyclines, as assessed by medical history and physical examination, were excluded. After screening 85 consecutive individuals, 40 subjects were invited to participate, gave written informed consent, and were enrolled into this parallel-arm, randomized clinical trial.

After a baseline visit where clinical and biological parameters were collected, patients were randomized (random permuted block approach) to receive either an IPT or control SPT. All individuals received oral hygiene instructions. Allocation to treatment was concealed in an opaque envelope opened by the therapist after completion of the common component of the treatment. Standard periodontal therapy involved only scaling and root planing consisting of one session (4-6 hours) of full-mouth subgingival instrumentation of the diseased dentition by means of a piezoceramic device (Piezon Master 400, EMS, Nyon, Switzerland) under local anesthesia. Intensive periodontal therapy consisted of mechanical scaling and root planing as detailed for the SPT group and adjunctive local delivery of minocycline microspheres (Arestin, OraPharma, Warminster, Pa). In the IPT group, the average total dose of locally applied minocycline was 80 ± 25 mg per patient at the treatment session only. This antibiotic formulation was chosen because of its unique controlled delivery platform (microspheres) giving prolonged (21-day period) high concentrations of minocycline in the periodontal pockets without detectable systemic exposure.[11] Patients were reexamined 2 and 6 months after therapy and received only oral hygiene reinstructions.

Serial blood samples were collected before and 1, 2, and 6 months after therapy and assessed for C-reactive protein (CRP) (immunoturbidimetric assay, Cobas Integra, Roche Diagnostics, Mannheim, Germany; detection limit of 0.25 mg/L) and interleukin-6 (IL-6) serum concentrations (ELISA Quantikine HS, R&D System, Minneapolis, MN; detection limit 0.04 ng/L) in a blind fashion. Leukocyte counts (white blood cell [WBC]) and total (TC) and high-density lipoprotein cholesterol (HDL-C) were quantified using standard clinical pathology procedures.

Blood pressure was recorded at baseline and 2 and 6 months after the completion of periodontal therapy. Averaged consecutive triplicate readings were obtained with a semiautomatic Omron HEM-705CP oscillometric BP re-

Table II. Patient clinical characteristics

Parameter	Standard therapy				Intensive therapy			
	Baseline	2 mo	6 mo	*P*	Baseline	2 mo	6 mo	*P*
BMI, kg/m^2	25 ± 4 (24-28)	25 ± 4 (24-28)	25 ± 4 (24-28)	.8101	26 ± 4 (24-28)	25 ± 4 (23-27)	25 ± 5 (23-28)	.3682
Systolic BP, mm Hg	131 ± 16 (125-140)	128 ± 15 (121-136)	130 ± 17 (123-139)	.2379	135 ± 14 (129-143)	129 ± 17* (122-138)	135 ± 20 (127-146)	.0412
Diastolic BP, mm Hg	85 ± 11 (81-91)	84 ± 12 (80-91)	85 ± 9 (81-90)	.9862	86 ± 11 (82-91)	85 ± 12 (80-91)	86 ± 13 (81-93)	.8882
FMPS†	55 ± 20 (50-69)	9 ± 15* (7-21)	11 ± 12* (10-21)	<.0001	43 ± 23 (41-63)	10 ± 14* (9-22)	10 ± 11* (9-19)	<.0001
FMBS‡	67 ± 16 (61-76)	24 ± 9* (21-29)	29 ± 12* (26-37)	<.0001	74 ± 29 (60-73)	18 ± 12* (16-24)	22 ± 12* (20-31)	<.0001
PPK§	74 ± 29 (65-93)	16 ± 12* (13-24)	18 ± 12* (16-28)	<.0001	77 ± 25 (68-91)	17 ± 11* (15-15)	14 ± 9* (12-20)	<.0001

* $P < .01$ compared to baseline in the same group, Bonferroni post hoc ANOVA.
† Average full-mouth supragingival plaque scores.
‡ Average full-mouth gingival bleeding scores.
§ Average full-mouth number of periodontal lesions.

Table III. Changes in inflammatory and lipid markers

Parameter geometric mean ± SD (95% CI)	Standard therapy					Intensive therapy				
	Baseline	1 mo	2 mo	6 mo	*P*	Baseline	1 mo	2 mo	6 mo	*P*
WBC, 10^9/L	6.6 ± 1.6 (6.0-7.5)	5.6 ± 1.6* (5.0-6.6)	5.8 ± 2.0 (5.2-7.1)	6.0 ± 1.8 (5.4-71)	.0209	7.3 ± 2.2 (6.6-8.6)	6.2 ± 1.3† (5.4-7.5)	6.2 ± 1.9† (5.5-7.4)	6.5 ± 2.0† (5.9-7.7)	.0137
CRP, mg/L	2.2 ± 2.2 (1.8-3.9)	2.4 ± 2.6 (2.1-4.6)	2.1 ± 2.4 (1.7-4.0)	2.5 ± 1.4 (1.4-3.7)	.0039	1.8 ± 1.1 (1.6-2.7)	1.9 ± 3.0* (1.1-3.9)	1.6 ± 2.0* (1.1-2.9)	1.1 ± 1.4* (0.8-2.2)	.0009
IL-6, ng/L	1.5 ± 1.0 (1.4-2.3)	1.8 ± 1.0 (1.6-2.6)	1.6 ± 1.1 (1.4-2.4)	1.0 ± 0.9 (0.9-1.8)	.0755	1.3 ± 0.9 (1.1-1.9)	1.0 ± 0.8† (0.9-1.6)	0.8 ± 06† (0.8-1.3)	0.8 ± 0.6* (0.7-1.2)	.0021
TC, mg/dL	209 ± 23 (197-221)	209 ± 31 (194-225)	209 ± 31 (197-225)	201 ± 23 (194-217)	.2756	209 ± 27 (197-224)	201 ± 31* (190-217)	201 ± 23† (198-213)	197 ± 23† (186-209)	.0384
LDL-C, mg/dL	128 ± 23 (116-139)	132 ± 27 (120-147)	128 ± 27 (116-143)	120 ± 27 (108-136)	.3352	132 ± 23 (120-143)	120 ± 27* (112-136)	124 ± 19* (116-132)	116 ± 19† (108-124)	.0082
HDL-C, mg/dL	50 ± 16 (46-62)	50 ± 16 (46-62)	50 ± 19 (46-62)	54 ± 16† (50-66)	.0245	54 ± 16 (46-62)	54 ± 16 (46-62)	50 ± 16 (46-62)	54 ± 16 (50-62)	.6723
Triglycerides, mg/dL	142 ± 98 (98-186)	133 ± 53 (98-142)	142 ± 80 (98-168)	133 ± 71 (87-160)	.7097	124 ± 98 (80-168)	115 ± 87 (80-160)	124 ± 71 (87-151)	124 ± 71 (87-160)	.8401

* $P < .05$ compared to baseline in the same group, Bonferroni post hoc ANOVA.
† $P < .01$ compared to baseline in the same group, Bonferroni post hoc ANOVA.

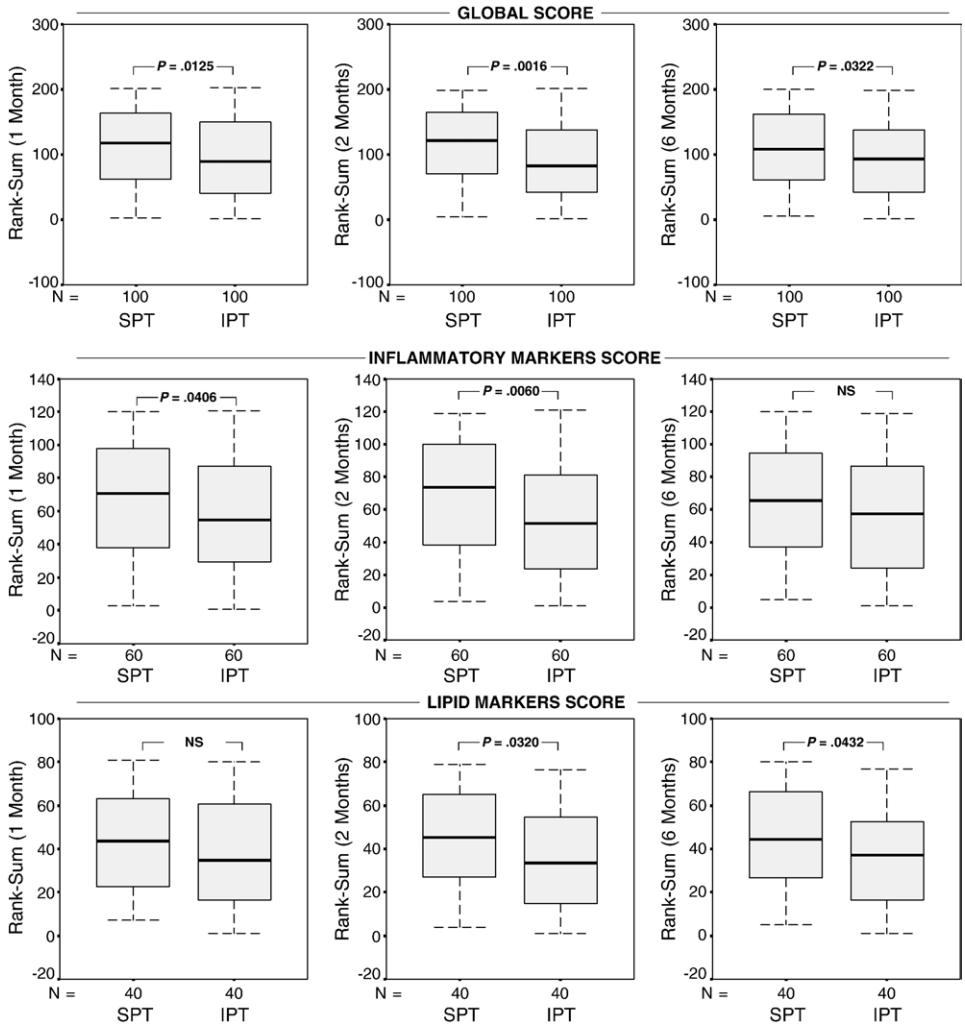
corder. Individuals rested for 5 minutes sitting in a semi-reclined position on the dental chair of the research center, after which BP recordings were performed.[12] Body mass index was calculated as weight divided by the square of height (kilograms per meter squared). Framingham risk scores were calculated with a dedicated software (CardioRisk Manager, British Medical Journal Books, London, UK).[13]

Statistical analysis

Data are reported as geometric mean ± SD and 95% CI intervals unless otherwise specified. Differences between the 2 treatment groups at baseline were assessed by Student *t* test for continuous and χ^2 test for categorical variables. An intention-to-treat, last-observation-carried-forward data analysis was performed in a conventional manner (analysis of variance [ANOVA] for repeated measurements between groups) with post hoc comparison made by Bonferroni test. For correlation analysis, the Spearman's rank correlation coefficient was calculated for changes in clinical and laboratory variables. Data were also analyzed using a multiple end-point statistical approach (O'Brien nonparametric rank-sum test) anticipating the nonnormal distribution and correlation of most of the outcome measures.[14-16]

In particular, we investigated the treatment effect across global scores for inflammatory and lipid outcomes (CRP, IL-6, WBC, TC, and HDL-C). A specific inflammatory score (CRP,

Figure 1



Box-and-whisker plots showing changes in rank-sum global, inflammatory, and lipid scores (O'Brien global test statistics) by treatment group at 1, 2, and 6 months after periodontal therapy. The box refers to the 25th (bottom) and 75th (up) rank-sum percentiles, and the median is the horizontal line inside.

IL-6, WBC) was designed to incorporate changes (decreases) in each marker taken on the same patient after therapy. Furthermore, a lipid score (TC and HDL-C) reflected changes (reduction in TC and increase in HDL-C) in traditional cardiovascular risk factors. A global score (sum of inflammatory and lipid scores) was also calculated. Patients were ranked on each of the outcomes (difference between baseline and follow-up visits divided by baseline) as previously described.[15] A secondary analysis (Mann-Whitney U test) to understand the relative contribution of each individual variable to the global scores was conducted. P values $<0 \cdot 05$ were deemed significant. All calculations were performed using a statistical application software (SAS, version 8.2, SAS Institute, Cary, NC).

Results

We did not observe significant differences in subject characteristics by treatment group (20/arm) at baseline (Table I). All subjects completed the trial and attended at each visit. No adverse effects were reported in either group over the study period.

Table II summarizes baseline and changes in clinical (medical and periodontal) parameters of all individuals after 2 and 6 months of therapy. Subjects did not show significant changes in BMI (0.4 ± 1.27 kg/m^2 difference 95% CI -2.2 to 2.8 between treatment groups at 2 months and 0.2 ± 1.4 kg/m^2 95% CI -2.6 to 2.9 at

6 months, P = ns) nor did they report any changes in diet, habits, exercise, or medical treatments when asked by the examining clinician. Periodontal clinical parameters were significantly improved at all follow-up assessments. Average full mouth supra-gingival plaque and gingival bleeding scores decreased similarly in both groups after 2 months of therapy and remained lower than baseline up to 6 months (Table II). Individuals in the IPT group exhibited some additional reduction in gingival bleeding scores (P = .0562) compared to SPT patients only after 2 months of therapy.

When the effects of IPT and SPT on arterial BP were compared, the IPT group showed a reduction in systolic BP after 2 months of therapy (Table II). Further, a mean difference of 7 ± 3 mm Hg in systolic BP (95% CI 1-12, P = .0211) with respect to SPT was recorded. This difference was 14 ± 5 mm Hg (95% CI 3-25, P = .0124) for smokers, whereas it was smaller in magnitude at 6 months (−3 ± 4 mm Hg for nonsmokers and 13 ± 7 mm Hg for smokers, P = .0700). No changes in diastolic BP were observed.

Laboratory results for each group are presented in Table III. After 1 month of therapy, significant decreases in total WBC were observed for both groups (P < .05). In the IPT group, WBC decreased further at 2 (P < .01) and 6 (P < .01) months after therapy.

Intensive periodontal therapy produced significant reductions in inflammatory markers (IL-6 and CRP) and lipid markers (TC and low-density lipoprotein cholesterol [LDL-C]) (Table III) at all study visits, but no changes were observed in the SPT group. Mean decreases of 0.3 ± 0.4 ng/L (95% CI 0.1-0.6, P = .0343), 0.3 ± 0.6 ng/L (95% CI 0.1-0.7, P = .0023), and 0.4 ± 0.9 ng/L (95% CI 0.2-1.0, P = .0134) in IL-6 were observed at 1, 2, and 6 months in the IPT group, respectively. Mean decreases of 0.5 ± 0.7 mg/L (95% CI 0.1-1.2, P = .0342), 0.6 ± 1.0 mg/L (95% CI 0.2-0.8, P = .0003), and 0.6 ± 2.0 mg/L (95% CI 0.2-1.1, P = .0356) were observed at all three follow-up visits for CRP within the same group.

Exploratory analyses were performed to assess whether the observed changes in serum markers of inflammation and BP were associated with changes in clinical periodontal parameters as well as with changes in lipid levels. In the IPT group the decrease in systolic BP at 2 months correlated with a decrease in gingival bleeding score, a sensitive measure of resolution of the local infection (r = 0.48, P = .0232). In the same group the decrease in IL-6 correlated with a decrease in total and LDL cholesterol (r = 0.47, P = .0343; r = 0.68, P < .01) after 6 months, and the magnitude of its decrease correlated significantly with that of CRP (r = 0.63, P < .01).

Intensive periodontal therapy produced a greater effect on systemic parameters than control at each follow-up time point examined (1, 2, and 6 months after therapy) (Figure 1). Compared to the SPT control, IPT patients had significant decreases in inflammatory scores (CRP, IL-6, WBC) at 1 and 2 months, and in lipid markers scores (TC and HDL-C) at 2 to 6 months after treatment.

The IPT group exhibited greater reductions in IL-6 concentrations than control at 1 month (0.4 ± 0.2 ng/L difference, 95% CI 0.03-0.9, P = .0284) and 2 months (0.3 ± 0.2 ng/L difference, 95% CI 0.1-0.8, P = .0284). Greater reductions in CRP (0.4 ± 0.2 mg/L difference, 95% CI 0.01-0.8, P = .0438) and total cholesterol (0.3 ± 0.1 mmol/L difference, 95% CI 0.04-0.6, P = .0254) were observed comparing IPT to SPT at 2 months.

The whole population presented a decrease in Framingham risk scores at 2 and 6 months. Intensive periodontal therapy subjects had a greater mean reduction of 1.53% ± 1.20% (95% CI 1.05-2.24, P = 0.0290) and 2.00% ± 1.42% (95% CI 0.98-4.09, P = .0568) of absolute 10-year cardiovascular risk at 2 and 6 months, respectively, compared to control.

Discussion

These data indicate that severe generalized periodontitis caused a chronic systemic inflammatory response, and changes in serum cholesterol and systolic BP in these patients.

However, because of the small number of patients examined and the severe, generalized nature of the periodontitis caution is warranted in generalizing these data to all patients affected by periodontitis. Previous association studies have established a dose-dependent effect between the extent and severity of periodontitis and cardiovascular events.[17,18] This study does not establish the level of local periodontal infection that is capable of having a systemic effect. Larger studies including a wider spectrum of disease presentation will be necessary to better define the periodontitis subjects in whom the local infection causes significant systemic inflammation.

The aim of this investigation was to explore the effect of periodontitis on a cluster of traditional and novel cardiovascular risk factors such as lipid levels and systemic inflammatory markers including WBC. We chose a global statistical approach to ascertain whether the treatment used had any impact on these markers. C-Reactive protein and IL-6 serum concentrations are very sensitive, and reliable markers used to assess the individual systemic inflammatory burden. Both markers have also been independently defined as good predictors of future developments of serious systemic conditions (coronary artery events, insulin resistance and type-2 diabetes, hypertension). White blood cell count is known as a crude marker of systemic inflammation, and it correlates well with the host response to a variety of stimuli.[19] This marker has also been associated with a significant prediction of future cardiovascular events and glucose intolerance in different populations.[20-22] Independent of

which therapy was performed, individuals in our study showed a significant reduction of WBC already after 1 month, and such effect persisted up to 6 months after therapy. No differences, however, were noted between treatment regimens in terms of this parameter. The IPT group clearly showed a greater systemic anti-inflammatory effect (decrease in IL-6 and CRP). These 2 markers were also highly correlated.[23] The reduction of inflammatory markers was also associated with a decrease in total and LDL cholesterol, suggesting for the first time a potential effect of periodontitis-driven systemic inflammation on lipid metabolism.

Lipid markers such as total and HDL cholesterol have assumed crucial importance in the prediction of individual future risk for cardiovascular events.[24] Changes in concentrations of these markers, however, have also been associated with acute and chronic infections.[25] The present data suggest that severe periodontitis may represent one condition able to trigger lipid level alterations perhaps by eliciting an increased systemic inflammatory burden. Whether this finding is true or confounded by other important factors (diet, smoking, age) can only be ascertained by readdressing the question in further full-scale clinical intervention trials.

The changes in systolic BP observed after 2 months of IPT further strengthen the association between periodontitis and cardiovascular risk factors. This study noted a decrease in systolic BP at 2 months that correlated with the degree of reduction in gingival bleeding, a sensitive clinical marker of periodontal inflammation and infection. Only a few studies addressed the relation between BP and periodontal disease. Left ventricular mass in hypertensive patients and systolic BP have been positively associated with the severity of periodontitis.[10,26] The potential mechanisms underlying this association remain yet to be discovered. Periodontitis has been associated with a state of endothelial dysfunction and systemic inflammation.[27] Systemic low-grade inflammation, even that produced by bacterial endotoxin,[28] might affect the endothelial cells and thus reduce the local availability of vasodilating factors by (1) decrease in intrinsic NO production,[29] (2) increase in NO degradation through an elevated production of O_2^- radicals,[30] (3) increased production of Cox-derived prostanoids which manifest potent contracting activity.[31] More research, however, is needed to establish whether cytokine elevation in chronic inflammation is the cause rather than the consequence of the increase in BP observed in these patients. Moreover, metabolic changes (insulin resistance) often found in patients who have periodontitis[32] might represent another potential mechanism behind the link between higher systolic BP and periodontitis.[9,33,34] At this stage, hypotheses to explain this relationship can only be speculative. Inflammatory markers are highly correlated with measures of obesity, systolic BP, HDL-C, fasting glucose, and insulin sensitivity.[35] Systemic inflammation in response to severe periodontitis might promote both insulin resistance and dyslipidemia. IL-6 produced at inflamed periodontal tissues may play a prominent role in linking periodontitis, endothelial dysfunction, and cardiovascular risk.[33] Further research is needed to evaluate this hypothesis.

In the IPT group, local delivery of minocycline in the periodontal pockets (the sites of infection) was used to supplement the antibacterial action of scaling and root planing by allowing the achievement and maintenance of high concentrations of the antibiotic into the periodontal pockets and thus eradicate the periodontal pathogens[36,37] and to do so without reaching detectable levels in serum.[11] Our hypothesis was that a better control of the local infection would then induce a greater reduction of the systemic acute phase response. This group preliminary proposed that SPT is also capable of such effect but only after 6 months.[38] These data confirm that observation. The SPT group showed a reduction in most of the markers examined after 6 months. The IPT group instead reached those levels earlier: already 2 months after treatment. Tetracyclines are known to exert an anti-inflammatory effect.[39,40] Our data, however, do not provide evidence on whether the benefit of using local minocycline was due to antibacterial or anti-inflammatory properties.

The observation that cardiovascular risk factors might be influenced by periodontitis may have important clinical consequences. First, as inflammation plays an important role in the pathophysiology of various conditions (metabolic syndrome, BP, vascular health),[34] the association of mild chronic inflammation with future serious events in observational studies[41] may be influenced by an underlying severe periodontal infection. Second, periodontitis may increase the risk of future cardiovascular events because of the pro-atherogenic changes (increased cholesterol) and increased systolic BP induced in affected individuals. Cigarette smoking represents the major influential factor with regard to the association between periodontal infections and systemic inflammation, and this preliminary investigation raises the hypothesis of a possible interaction of smoking, periodontal infection, and systolic BP on systemic health.

Third, if periodontitis were the major inflammatory stimulus in at least some patients with periodontitis, severe periodontal infections may represent a major etiologic factor for atherosclerosis, metabolic syndrome, and their sequelae.

The significance of periodontitis as a cause of systemic inflammation and, potentially, disease has to

be discussed in the context of the high prevalence of chronic periodontitis which affects in mild forms up to 40% and in more severe forms a good 10% of the adult population.

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