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Influence of periodontal intervention therapy on risk of cardiovascular disease

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Cardiovascular disease and periodontal disease are both chronic inflammatory diseases. Numerous cross-sectional and longitudinal epidemiological studies have provided evidence that there is an association between periodontitis and elevated risk for cardiovascular disease (1, 4, 5, 9, 10, 33, 34, 39, 56, 78, 100, 124). Some of these studies have shown that periodontitis is an independent risk factor for cardiovascular disease even after adjusting for traditional cardiovascular factors such as age, gender, smoking, obesity and blood lipids. In addition, experimental evidence has shown that periodonto-pathogenic bacteria, mainly *Porphyromonas gingivalis*, play a role in atherogenesis (18, 21, 32, 46, 52, 70, 72, 121). A number of systematic reviews and meta-analyses have described the relationship between periodontal infection and cardiovascular disease, and have suggested that periodontitis may contribute to cardiovascular disease and stroke in susceptible subjects (8, 62, 67, 82, 88, 97).

Periodontitis shares a number of common risk factors with cardiovascular disease, such as age, male gender, socio-educational status, and, most importantly, smoking. Therefore the question arises as to what the nature of the association between periodontitis and cardiovascular disease is. Does it arise because of interaction between confounding factors such as smoking, or is it causal in nature? The answers are unclear at present. Recent studies have focused on the systemic effect of periodontal intervention on surrogate indicators of cardiovascular disease, such as serum markers of inflammation, serum lipid levels, measurements of endothelial function and haemostatic factors. If the association between periodontal infection and cardiovascular disease is causal, effective periodontal treatment should lead to improvement of systemic inflammation load, lipid profiles and endothelial function. Thus successful periodontal treatment could lower the risk of cardiovascular events or even prevent onset and progression of the disease. This review focuses on the influence of periodontal intervention treatment on the risk factors for cardiovascular disease.

Influence of periodontal intervention on serum lipid profiles

It is well accepted that hyperlipidemia is a risk factor for coronary heart disease. Serum total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglycerides are conventional lipid biomarkers used to evaluate the lipid profiles of an individual. LDL-C, which contains a single apolipoprotein (apoB-100), is the major atherogenic cholesterol. An elevated serum LDL-C level is recognized as a major cause of coronary heart disease (89). HDL-C is considered to be anti-atherogenic. The major apolipoproteins in HDL are apoA-I and apoA-II. The levels of HDL-C are inversely correlated with risk for coronary heart disease (89). Several meta-analyses have shown that raised triglyceride is also an independent risk factor for coronary heart disease (6, 7), but elevated triglyceride levels are commonly associated with other lipid and non-lipid factors (89). Guidelines for the detection, evaluation and treatment of hyperlipidemia, and the classification and implication of total cholesterol, LDL-C, HDL-C and triglyceride levels are listed in Table 1.

Recent studies have shown an association between periodontitis and elevated atherogenic lipid fraction

Table 1. Classification* and implication of total cholesterol, LDL-C, HDL–C and triglyceride levels

Lipid biomarker	Levels (mg ⁄ dl)	Category	Implication
Total cholesterol	<200	Desirable	–
	200–239	Borderline high	–
	≥240	High	–
LDL	<100	Optimal	Very low risk of CHD
	100–129	Near optimal ⁄ above optimal	Atherogenesis occurs
	130–159	Borderline high	Atherogenesis proceeds at a significant rate
	160–189	High	Atherogenesis markedly accelerated
	≥190	Very high	
HDL	<40	Low	Independent risk factor for CHD
	≥ 60	High	Reduced risk for CHD
TG	<150	Normal	–
	150–199	Borderline high	–
	200–499	High	Heightened CHD risk substantially beyond that predicted by LDL-C alone

*According to the National Cholesterol Education Program guidelines for the detection, evaluation and treatment of hyperlipidemia (89).
LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triglyceride; CHD, coronary heart disease.

levels and ⁄ or decreased anti-atherogenic lipid fraction levels (40, 63–66, 87, 90, 91, 109, 112, 118, 124). Most of these were cross-sectional studies, and it is still unclear whether there is a causal relationship between periodontitis and hyperlipidemia. Improvement of serum lipid profiles after periodontal treatment may indicate a causal relationship between periodontitis and hyperlipidemia, and may suggest the possibility of reducing the risk of coronary heart disease by effective periodontal intervention.

A number of intervention studies have evaluated alterations in serum lipid levels after periodontal treatment. As expected, periodontal parameters improved significantly after various therapies in all studies. Interestingly, serum lipid profiles also improved after periodontal treatment in many of the studies, although the markers that were altered and the degree of improvement varied greatly. One reason for this variability is that the subjects included in these studies differed in terms of their general health status with regard to hyperlipidemia, hypertension or other cardiovascular diseases.

Table 2 shows the effects of intervention studies on alteration of serum lipid markers in systemically healthy patients. Total cholesterol and LDL-C levels decreased after periodontal therapy in two randomized controlled trials (26, 28). Two periodontal regimens, mechanical periodontal treatment and mechanical debridement with adjunctive local delivery of minocycline (intensive periodontal treatment), were compared for their effect on lipid profiles and other biomarkers at 1, 2 and 6 months after therapy (28). Intensive periodontal treatment produced significant reductions in total cholesterol and LDL-C levels. The results indicated that mechanical periodontal treatment with local delivery of antibiotics produced improvement in lipid profiles. HDL-C levels were significantly increased 3 months after periodontal intervention in three prospective studies (64, 101, 102). In addition, the structure and metabolism of HDL had also changed in an anti-atherogenic direction after periodontal treatment (101). These results suggested that periodontitis may diminish the anti-atherogenic potency of HDL, thus increasing the risk for coronary heart disease, and that periodontal treatment could improve this situation.

In some studies, however, significant improvement in traditional lipid markers was not achieved after periodontal treatment (37, 54, 76, 99, 111). This may be due to the relatively low levels of atherogenic cholesterols and high levels of HDL-C at baseline, as shown in Table 2. In one of these studies, a significant

Table 2. Effect of periodontal intervention studies on lipid markers in otherwise healthy subjects

Reference	Study design and time points for measurements	Lipid markers measured	Alteration of lipid markers		
			Baseline value for each group	NCEP classification at baseline**	Levels of lipid markers with significant improvement ($P < 0.05$) after treatment
D'Aiuto et al. (2005) (26)	Test group (n = 20): SRP + local delivery of minocycline; control group A (n = 24): no treatment; control group B (n = 21): SRP only. Baseline and 2 months after treatment	TC, LDL-C, HDL-C, TG (mmol/l)	TC: 5.5 ± 0.7; 5.4 ± 0.7; 5.3 ± 0.7 (212.3 ± 27.0; 208.4 ± 27.0; 204.6 ± 27.0)* LDL-C: 3.4 ± 0.6; 3.2 ± 0.6; 3.2 ± 0.6 (131.2 ± 23.2; 123.6 ± 23.2; 123.6 ± 23.2)* HDL-C: 1.5 ± 0.5; 1.3 ± 0.5; 1.3 ± 0.5 (57.9 ± 19.3; 50.2 ± 19.3; 50.2 ± 19.3)* TG: 1.4 ± 1.1; 1.7 ± 1.1; 1.7 ± 1.1 (123.9 ± 97.3; 150.4 ± 97.3; 150.4 ± 97.3)*	TC borderline high; LDL-C near optimal to borderline high; HDL-C low to high; TG normal to borderline high	TC: 5.2 ± 0.7 (test); 5.4 ± 0.9 (control B) The significant within-group decreases in TC and LDL-C levels were in the SRP + local delivery of minocycline group
D'Aiuto et al. (2006) (28)	Test group (n = 20): SRP + local delivery of minocycline; control group (n = 20): SRP only Baseline, 1, 2 and 6 months after treatment	TC, LDL-C, HDL-C, TG (mg/dl)	TC: 209 ± 27; 209 ± 23 LDL-C: 132 ± 23; 128 ± 23 HDL-C: 54 ± 16; 50 ± 16 TG: 124 ± 98; 142 ± 98	TC borderline high; LDL-C near optimal to borderline high; HDL-C low to high; TG normal	TC: 197 ± 23; 201 ± 23 LDL-C: 116 ± 19; 120 ± 27
Pussinen et al. (2004) (101)	Test group (n = 30): mechanical therapy and antibiotics if indicated; no control group Baseline and 3 months after treatment	TC, HDL-C, TG (mmol/l)	TC: 6.28 ± 1.18 (242.5 ± 45.6)* HDL-C: 1.40 ± 0.40 (54.1 ± 15.44)* TG: 1.55 ± 0.65 (137.2 ± 57.5)*	TC high; HDL-C low to high; TG normal	HDL-C: 1.55 ± 0.41
Pussinen et al. (2004) (102)	Test group (n = 30): mechanical periodontal treatment, and gingivoplasty or antibiotics if indicated; no control group Baseline and 3 months after treatment	TC, HDL-C, TG (mmol/l), HDL/LDL ratio, oxidized LDL (mU/l), LDL particle size (nm), LDL oxidation lag time, LDL maximal dienes	TC: 6.51 ± 1.29 (251.4 ± 49.8)* HDL-C: 1.30 ± 0.19 (50.2 ± 7.3)* TG: 1.74 ± 0.63 (154.0 ± 55.8)* HDL/LDL ratio: 0.31 ± 0.01 LDL particle size: 21.7 ± 0.37 LDL oxidation lag time: 66.6 min LDL maximal dienes: 42.3 µmol/mg	TC high; HDL-C low to high; TG borderline high	HDL-C: 1.48 ± 0.28 HDL/LDL ratio: 0.34 ± 0.10 LDL particle size: 21.9 ± 0.37

Table 2. (*Continued*)

Reference	Study design and time points for measurements	Lipid markers measured	Alteration of lipid markers		
			Baseline value for each group	NCEP classification at baseline**	Levels of lipid markers with significant improvement ($P < 0.05$) after treatment
Kallio et al. (2008) (64)	Test group (n = 34): OHI, SRP and periodontal flap surgery if indicated; no control group Baseline and 6 months after treatment	TC, HDL-C, TG, LDL-C (mmol/l), ApoAI (g/l)	TC: 5.3 ± 1.0 (204.6 ± 38.6)* LDL-C: 3.33 ± 0.94 (128.6 ± 36.3)* HDL-C: 1.28 ± 0.38 (49.4 ± 14.7)* TG: 1.57 ± 1.13 (138.9 ± 100)* ApoAI: 1.52 ± 0.32	TC borderline high; LDL-C near optimal; HDL-C low to high; TG normal	HDL-C: 1.33 ± 0.40 ApoAI: 1.63 ± 0.38
Löscher et al. (2005) (76)	Test group (n = 32): OHI, supragingival scaling and polishing, root planing; no control group Baseline and 3 months after treatment	TC, LDL-C, HDL-C, TG (mmol/l), Lp-PLA_2 activity (μmol/ml/h)	TC: 5.01 (193.4)* LDL-C: 3.14 (131.2)* HDL-C: 1.27 (49.0)* TG: 1.36 (120.4)* Lp-PLA_2: 3.606 ± 0.986	TC desirable; LDL-C borderline high; HDL-C low to high; TG normal	Lp-PLA_2: 3.295 ± 0.945
Seinost et al. (2005) (111)	Test group (n = 30): conservative non-surgical periodontal treatment; control group (n = 31): periodontally healthy, no treatment Baseline and 3 months after treatment	TC, LDL-C, HDL-C, TG (mg/dl)	TC: 207 ± 35; 203 ± 39 LDL-C: 123 ± 33; 133 ± 33 HDL-C: 69 ± 19; 61 ± 13 TG: 84 ± 50; 88 ± 48	TC borderline high; LDL-C borderline high; HDL-C high; TG normal	No significant differences
Elter et al. (2006) (37)	Test group (n = 22): SRP, periodontal flap surgery if indicated, and extraction of hopeless teeth; no control group Baseline, 1 month before treatment and 1 month after treatment	TC, HDL (mg/dl)	TC: 227 ± 30 HDL-C: 64 ± 17	TC borderline high; HDL-C high	No significant differences

Table 2. (*Continued*)

Reference	Study design and time points for measurements	Lipid markers measured	Alteration of lipid markers		
			Baseline value for each group	NCEP classification at baseline**	Levels of lipid markers with significant improvement ($P < 0.05$) after treatment
Pischon et al. (2007) (99)	Test group (n = 21): OHI, SRP and antibiotic therapy; no control group Baseline, following OHI, following last session of SRP, 2 months after SRP and before antibiotic treatment, 3 months after antibiotic treatment, 6 months after antibiotic treatment	TC, LDL-C, HDL-C, TG (mg/dl)	TC: 199.4 ± 40.9 LDL-C: 118.5 ± 31.8 HDL-C: 60.2 ± 14.9 TG: 103.8 ± 55.1	TC desirable; LDL-C near optimal; HDL-C high; TG normal	No significant differences
Higashi et al. (2008) (54)	Test group (n = 16): OHI, SRP and antibiotic therapy; control group 1 (n = 20): without periodontitis; control group 2 (n = 16): untreated periodontitis Baseline and at 24 weeks of follow-up	TC, LDL-C, HDL-C, TG (mg/dl)	TC: 4.61 ± 0.68 (178.0 ± 26.3)* TG: 1.24 ± 0.58 (109.73 ± 51.3)* HDL: 1.19 ± 0.48 (45.9 ± 18.5)* LDL: 2.60 ± 0.63 (100.4 ± 24.3)* ***	TC desirable; LDL near optimal; HDL low to high; TG normal	No significant differences

*The values in parentheses were converted from mmol/l to mg/dl to allow comparison with data in Table 1.
**According to the National Cholesterol Education Program (NCEP) guidelines for the detection, evaluation and treatment of hyperlipidemia (89).
OHI, oral hygiene introduction; SRP, subgingival scaling and root planing; TC, total cholesterol; LDL-C, low- density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; Ox-LDL, oxidized low-density lipoprotein; ApoAI, apolipoprotein AI; Lp-PLA_2, lipoprotein-associated phospholipase A_2.
*** Patients with periodontitis, test group + control group 2, n = 32.

reduction in a novel lipid marker, Lp-PLA_2, was observed 3 months after effective periodontal treatment (76). Lp-PLA_2 binds to LDL in the circulation and can hydrolyse the most atherogenic form of LDL (i.e. oxidized LDL) into lysophosphatidyl choline and oxidized fatty acids, which are pro-inflammatory mediators and may contribute to the development of atherosclerotic lesions. Lp-PLA_2 has been shown to be an independent risk factor for cardiovascular disease (14, 20, 93). Thus, reduction in the plasma levels of Lp-PLA_2 may indicate a positive effect of periodontal treatment on systemic lipid profiles.

Table 3 lists the periodontal intervention studies performed on periodontitis patients with hyperlipidemia or proven cardiovascular diseases. In hyperlipidemic patients without any medical control of blood lipids, mechanical periodontal treatment resulted in a significant decrease in serum levels of total cholesterol, LDL-C (35, 92) and triglyceride, as well as an increase in levels of HDL-C (35) at 3 months after treatment. It is worth noting that, in these two studies, the levels of lipid markers before treatment were high or borderline high, according to the National Cholesterol Education Program guidelines for the detection, evaluation and treatment of hyperlipidemia (89), which indicates a relatively high risk of coronary heart disease. Moreover, no significant changes in the levels of total cholesterol, LDL-C or triglyceride were observed after periodontal treatment in a study by Tüter et al. (120), in which all patients were taking statins. In this study, the baseline levels of total cholesterol, LDL-C and triglycerides were within normal limits or at a borderline high level as defined by the National Cholesterol Education Program guidelines for the detection, evaluation and treatment of hyperlipidemia. However, the baseline level of HDL-C was low (<40 mg/dl), which indicates an increased risk of coronary heart disease, and the levels of HDL-C and apoA were significantly improved after treatment. Further, Tüter et al. (120) compared the impact of scaling and root planing alone and the adjunctive application of a sub-antimicrobial dose of doxycycline on lipid profiles. The results showed a greater improvement in levels of HDL-C and apoA in the doxycycline group. However, in studies by Higashi et al., although the subjects had hypertension (54) or other cardiovascular diseases (53), their baseline levels of total cholesterol, LDL-C and triglyceride were all within normal limits, and none of them showed a significant change after periodontal treatment. We therefore speculate that the improvement in lipid profiles after periodontal treatment may be associated with the baseline levels of lipid biomarkers.

In addition to traditional lipid biomarkers, Montebugnoli et al. (86) found a significant decrease in oxidized LDL at 3 months after periodontal treatment in patients with both periodontitis and cardiovascular disease. The oxidative modification of LDL is recognized as a key step in the initiation and progression of atherosclerosis, and elevated circulating levels of oxidized LDL are associated with high coronary heart disease risk (55, 57). The improvement of oxidized LDL levels after periodontal therapy might suggest a relationship between oxidative modification of lipids and periodontitis, and reversal of the elevated oxidized LDL as a result of periodontal treatment.

Many factors may influence the results of an intervention study, such as age, gender, current smoking, medication, etc., and most of the randomized controlled trials reviewed above took these factors into consideration (26, 28, 53, 54, 92, 111, 120). In non-randomized controlled trials (35, 37, 64, 76, 99, 101, 102), the subjects were advised not to change their smoking habits, diet and medication. Baseline levels of blood lipids may be an important factor as lipid variables within normal limits before treatment are less likely to show significant improvement after periodontal intervention. In addition, adjunctive application of antibiotics with mechanical periodontal treatment seems have a beneficial effect on the lipid profile. The duration of follow-up may also be a potential influencing factor. However, because of the limited sample size and heterogenity of the studies, statistical analysis of these discrepancies is not feasible. Nevertheless, based on these intervention studies, a preliminary conclusion could be drawn that there may be a causal link between periodontal disease and impaired serum lipid profiles, and lipid levels may improve after periodontal treatment in periodontitis patients with hyperlipidemia. Nonetheless, further investigations are needed in this field.

The mechanisms of the relationships between periodontitis and lipid profiles are still unclear. Early reviews noted that periopathogenic bacteria and their components, for example lipopolysaccharide, may gain access to the circulation, thus activating the immune response and altering the levels of pro-inflammatory cytokines and serum lipids (24, 58). Among the intervention studies reviewed above, several performed a correlation analysis between lipid markers and other variables before periodontal treatment (64, 76, 92, 101, 102). Some of these studies showed a significant correlation between lipid-related parameters and pro-inflammatory cytokines or lipo-

Table 3. Periodontal intervention studies in subjects with hyperlipidemia or proven cardiovascular disease

Reference	Study design and time points for measurement	Lipid markers measured	Alteration of lipid markers		
			Baseline value for each group	NCEP classification at baseline**	Levels of lipid markers with significant improvement ($P < 0.05$) after treatment
Oz et al. (2007) (92)	Hyperlipidemia Test group (n = 25): mechanical treatment and open flap debridement if indicated; control group (n = 25): no treatment Baseline and 3 months after treatment	TC, LDL-C, HDL-C, TG, VLDL (mg/dl)	TC: 244.88 ± 21.22; 237.28 ± 24.20 LDL-C: 155.22 ± 19.02; 146.63 ± 14.82 HDL-C: 53.4 ± 10.04; 53.86 ± 11.21 TG: 181.28 ± 91.79; 175.88 ± 54.03 VLDL: 36.25 ± 18.35; 36.77 ± 12.07	TC high; LDL-C borderline high; HDL-C low to high; TG borderline high	TC: 213.6 ± 32.59; 222.88 ± 30.37 LDL-C: 115.8 ± 37.07; 142.95 ± 19.93
Duan et al. (2009) (35)	Hyperlipidemia Test group (n = 20): initial periodontal treatment; no control group Baseline and 3 months after treatment	TC, LDL-C, HDL-C, TG (mg/dl)	TC: 225.87 ± 5.79 LDL-C: 96.53 ± 6.56 HDL-C: 44.78 ± 2.70 TG: 175.22 ± 7.08	TC borderline high; LDL-C optimal; HDL-C low to high; TG borderline high	TC: 214.7 ± 5.0 HDL-C: 51.73 ± 2.3 TG: 155.8 ± 6.2
Tüter et al. (2007) (120)	Coronary heart disease Test group (n = 18): SRP + sub-antimicrobial dose of doxycycline; control group (n = 18): SRP only Baseline and 6 weeks after treatment	TC, LDL-C, HDL-C, VLDL-C, TG, ApoA, ApoB, lipoprotein A (mg/dl)	TC: 163.5; 153.5 LDL-C: 91.6; 85.1 HDL-C: 40.5; 38.0 TG: 149.0; 127.0 VLDL-C: 29.8; 25.4 ApoA: 119.0; 102.5 ApoB: 94.0; 78.0 Lipoprotein A: 25.5; 42.0	TC desirable; LDL-C optimal; HDL-C low; TG normal	HDL-C: 44.0; 38.0 ApoA: 128.5; 110.0 Lipoprotein A: 11.0; 14.0 Levels of HDL-C, apoA and lipoprotein A improved significantly in both groups. The increase of apoA and HDL-C was higher in the test group
Montebugnoli et al. (2005) (86)	Coronary heart disease Test group (n = 18): mechanical treatment; control group (n = 18): self-control, no treatment Baseline and 4 months after baseline without treatment as self-control, and 3 months after treatment	Ox-LDL (μg/l)	Baseline: 542.8 ± 597, 4 months after baseline without treatment: 514.5 ± 632	–	3 months after treatment: 444.5 ± 567

Table 3. (*Continued*)

Reference	Study design and time points for measurement	Lipid markers measured	Alteration of lipid markers		
			Baseline value for each group	NCEP classification at baseline**	Levels of lipid markers with significant improvement ($P < 0.05$) after treatment
Higashi et al. (2008) (54)	Hypertension Test group (n = 17): OHI, SRP and antibiotic therapy; control group A (n = 38): without periodontitis; control group B (n = 9): untreated periodontitis Baseline and 24 weeks of follow-up	TC, LDL-C, HDL-C, TG (mmol / l)	TC: 4.65 ± 0.88 (179.5 ± 34.0)* LDL-C: 2.46 ± 0.61 (95.0 ± 23.6)* HDL-C: 1.21 ± 0.50 (46.3 ± 19.3)* TG: 1.25 ± 0.61 (110.6 ± 54.0)* ***	TC desirable; LDL-C normal; HDL-C low to high; TG normal	No significant change
Higashi et al. (2009) (53)	Cardiovascular disease Test group (n = 24): OHI, SRP and antibiotic therapy; control group (n = 24): untreated. Baseline and 24 weeks of follow-up	TC, LDL-C, HDL-C, TG (mmol / l)	TC: 4.95 ± 1.25; 4.79 ± 1.21 (191.1 ± 48.3; 184.9 ± 46.7)* LDL-C: 2.88 ± 1.13; 2.93 ± 1.02 (111.2 ± 43.6; 113.1 ± 39.4)* HDL-C: 1.21 ± 0.62; 1.24 ± 0.73 (46.7 ± 23.9; 47.8 ± 28.2)* TG: 1.30 ± 0.79; 1.28 ± 0.73 (115.0 ± 69.9; 113.27 ± 64.6)*		

*The values in parentheses were converted from mmol / l to mg / dl to allow comparison with data in Table 1.**According to the National Cholesterol Education Program (NCEP) guidelines for the detection, evaluation and treatment of hyperlipidemia (89).
LDL, very low-density lipoprotein; ApoB, apolipoprotein B. Other abbreviations, see Table 2.
*** Patients with periodontitis, test group + control group B, n = 26.

polysaccharide concentration (64, 102). However, there are few studies on the correlation of these parameters after periodontal treatment. Nonetheless, D'Aiuto et al. (28) observed that a decrease in total cholesterol and LDL-C correlated with a decrease in interleukin-6 at 6 months after therapy. More studies are required to explore the mechanisms of the relationship between periodontitis and hyperlipidemia and the relationship between improvement of the lipid profile and periodontal therapy.

Influence of periodontal intervention on inflammatory markers

Acute-phase reactants

C-reactive protein

C-reactive protein is an acute-phase reactant that is primarily produced by the liver in response to infection or trauma. It is an important marker for systemic inflammation, and has been consistently found to be elevated in patients with coronary syndromes (3, 74, 103–105). It has been reported that elevated C-reactive protein levels in patients with unstable angina predict recurrent ischemic events (74). Indeed, serum C-reactive protein concentration is significantly increased in patients with coronary heart disease and myocardial infarction (3). In a large sample population study, it was noted that increasing levels of serum high-sensitivity C-reactive protein were associated with a risk of cardiovascular events, and that high-sensitivity C-reactive protein was the strongest univariate predictor of the risk of such events (103–105).

Recently, evidence has accumulated demonstrating the association between periodontitis and C-reactive protein. The serum C-reactive protein concentration is increased in systemically healthy subjects with periodontitis (16, 45, 75, 114). In a meta-analysis of case–control studies, it was found that subjects with periodontitis had 1.65 mg/l higher serum C-reactive protein concentrations compared to individuals without periodontitis (95). A number of studies have assessed the serum C-reactive protein levels in patients with cardiovascular disease or cardiovascular risk factors. The results show that periodontitis patients with cardiovascular disease or hypertension have significantly higher serum high-sensitivity C-reactive protein concentrations than patients without periodontitis (53, 54, 119). These studies indicate that periodontal disease is a chronic inflammatory disease resulting in elevation of serum C-reactive protein levels.

In recent years, some intervention trials have been performed to evaluate the effect of periodontal therapy on C-reactive protein levels in patients with periodontitis (Table 4). The subjects included in most studies were systemically healthy subjects with periodontitis. In addition, possible confounding factors were considered and compared, such as age, gender, race, diet, medication regimen and smoking status. In most studies, periodontal therapy resulted in an initial increase and then a significant reduction of serum C-reactive protein levels. However, there are some studies which have reported no significant changes. Tonetti et al. (117) found that levels of C-reactive protein increased significantly 24 h after periodontal treatment, and then decreased over the following 6 months, but this was not significantly different to baseline. On the other hand, a 6-week short-term study found no significant differences in C-reactive protein levels before and after treatment (59). D'Aiuto et al. (27) studied the effect of periodontal non-surgical therapy on systemic C-reactive protein levels. The results showed that there was no significant difference between levels before treatment and those 2 months after treatment, but the levels at 6 months were 0.5 mg/l lower compared with before treatment ($P < 0.05$). In other studies with observation periods of between 2 and 6 months, periodontal therapy resulted in a reduction of high-sensitivity C-reactive protein levels (16, 26, 28, 79). A recent meta-analysis on C-reactive protein in relation to periodontitis indicated that periodontal therapy lowers the levels of C-reactive protein by a weighted mean difference of 0.5 mg/l (95% CI 0.08–0.93, $P = 0.02$) (95).

The effects of periodontal therapy on C-reactive protein levels in periodontitis patients with coronary heart disease or cardiovascular risk factors have also been evaluated. Two pilot studies have shown that, in patients with coronary heart disease, C-reactive protein levels decreased significantly 6 weeks or 3 months after periodontal therapy (86, 120). In a very recent randomized-controlled trial (53), 48 patients with coronary heart disease who had periodontitis were randomly assigned to a periodontal treatment group or a control group (24 patients in each group). At 6 months after therapy, the serum concentration of high-sensitivity C-reactive protein was significantly reduced from 2.7 ± 1.9 to 1.8 ± 0.9 mg/l in the periodontal treatment group, but no significant reduction was noted in the control group

Table 4. Intervention trials on association between periodontitis and C-reactive protein

Reference	Study design and periodontal therapy	Number of subjects	Systemic health status	Time points for measurement	Concentrations of CRP (mg/l) ($P < 0.05$)	
					Baseline	After therapy
Mattila et al. (2002) (79)	Cohort study: Patients with CP: SRP, when indicated, metronidazole 500 mg bid for 7 days.	30	Healthy	Baseline, 6 weeks after completion of periodontal treatment	0.2–5.4	Decreased by 0.34 on average
D'Aiuto et al. (2004) (27)	Cohort study: Patients with CP: extraction of hopeless teeth, OHI, subgingival scaling and root planing	94	Healthy	Baseline, 2 and 6 months after completion of treatment	1.9 (3.6 IQR)	Median decrease between baseline and 6 months was 0.5 (95% CI 0.4–0.7)
Seinost et al. (2005) (111)	Control group: periodontal healthy, no treatment Test group: SRP, mouthwashes, systemic antibiotics	31/30	Healthy	Baseline and 3 months after periodontal treatment	0.8 ± 0.8 (control) 1.7 ± 1.6 (test)	1.1 ± 0.9
D'Aiuto et al. (2006) (28)	Control group: SRP Test group: SRP + local delivery of minocycline	20/20	Healthy	Baseline, 1, 2 and 6 months after periodontal treatment	1.8 ± 1.1 (control) 2.2 ± 2.2 (test)	1.1 ± 1.4 (control) 2.5 ± 1.4 (test)
Elter et al. (2006) (37)	Cohort study: Patients with CP: SRP, periodontal flap surgery where indicated, and extraction of hopeless teeth	22	Healthy	Baseline, 1 month after treatment	2.4 (3.3 IQR)	1.4 (2.8 IQR)
Blum et al. (2007) (16)	Control group: OHI Test group: OHI, SRP, systemic antibiotics	9/9	Healthy	Baseline and 3 months after treatment	2.97 ± 0.58 (test) 0.25 ± 0.14 (control)	2.33 ± 0.7 (test) 0.25 ± 0.14 (control)

Table 4. (*Continued*)

Reference	Study design and periodontal therapy	Number of subjects	Systemic health status	Time points for measurement	Concentrations of CRP (mg/l) ($P < 0.05$)	
					Baseline	After therapy
Pischon et al. (2007) (99)	Cohort study: Patients with CP: OHI, SRP, systemic antibiotics	21	Healthy	T1: baseline; T2: after OHI; T3: after last SRP; T4: 2 months after SRP; T5: 3 months after antibiotic treatment; T6: 6 months after antibiotic treatment	Significantly increased at T3 compared to T1. However, 8 weeks after SRP, median CRP values decreased to baseline levels and stayed low until the end of the study (shown graphically, no exact data presented)	
Kallio et al. (2008) (64)	Cohort study: Patients with CP: OHI, SRP and periodontal flap surgery if indicated	34	Healthy	Baseline and 6 months after periodontal treatment	2.17	1.76
Iwamoto et al. (2003) (61)	Cohort study: Patients with CP: 10 mg minocyclin HCl in each periodontal pocket and supragingival scaling once a week for a period of 1 month	15	Various systemic conditions at high risk for atherosclerosis (IGT, HT, Type 2 DM)	Before and after treatment	1677.0 ± 1740.7 (ng/ml)	934.3 ± 1000.2 (ng/ml)
Montebugnoli et al. (2005) (86)	Control group: 4 months without treatment Test group: OHI, supragingival scaling, polishing and subgingival debridement	18	Coronary heart disease	Baseline and 4 months after baseline without treatment or 3 months after periodontal treatment	4.32 ± 2.1 (control) 4.33 ± 2.0 (test)	3.42 ± 2.3 (test)
Taylor et al. (2006) (115)	Cohort study: Patients with advanced CP: full-mouth tooth extraction	67	Hyperlipidemia (n = 25), diabetes mellitus (n = 8), hypertension (n = 18)	T1: the day of presentation; T2: 1–2 weeks after acute treatment; T3: 12 weeks after dental clearance	T1: 2.5; T2: 2.3	T3: 1.8

Table 4. (*Continued*)

Reference	Study design and periodontal therapy	Number of subjects	Systemic health status	Time points for measurement	Concentrations of CRP (mg/l) ($P < 0.05$)	
					Baseline	After therapy
Lalla et al. (2007) (69)	Cohort study: Patients with CP: OHI, SRP, mouth wash twice daily for 2 weeks	10	Diabetes (seven type 1, three type 2)	Baseline and 4 weeks after treatment	2.3	1.5
Tüter et al. (2007) (119)	Control group: SRP Test group: SRP + sub-antimicrobial dose doxycycline	18/18	Coronary heart disease	Baseline and 6 weeks after periodontal treat-ment	The serum levels of hsCRP were significantly decreased in both groups (shown graphically, no exact data presented)	
Higashi et al. (2008) (54)	Test group: OHI, SRP and antibiotic therapy; Control group A: without periodontitis; Control group B: untreated peridontitis	16/20/16	Healthy	Baseline and 24 weeks after periodontal treatment	2.1 ± 1.9 (test); 0.9 ± 1.0 (control A)	1.3 ± 1.2
		17/38/9	Hypertensive		2.4 ± 2.2 (test); 1.1 ± 1.2 (control A)	1.4 ± 1.2
Higashi et al. (2009) (53)	Test group: OHI, SRP and antibiotic therapy; Control group A: without periodontitis; Control group B: untreated peridontitis	24/53/24	Coronary artery disease	Baseline and 24 weeks after periodontal treatment	2.7 ± 1.9 (test); 1.7 ± 1.1 (control A)	1.8 ± 0.9

CI, confidence interval; CP, chronic periodontitis; HT, hypertension; IGT, impaired glucose tolerance; IQR, interquartile range; Type 2 DM, Type 2 diabetes mellitus. Other abbreviations, see Table 2.

(from 2.6 ± 2.2 to 2.5 ± 2.1 mg/l). Similar results have been reported in our study on 32 chronic periodontitis patients with stable coronary heart disease (36). The serum high-sensitivity C-reactive protein levels decreased significantly from 2.7 ± 2.7 to 2.0 ± 2.1 mg/l ($P < 0.05$) at 3 months after periodontal therapy. The serum C-reactive protein concentrations were also reduced after periodontal therapy in periodontitis patients with hypertension (54). Taylor et al. (115) observed changes in systemic C-reactive protein levels after full-mouth tooth extraction in patients with various cardiovascular risk factors (such as hypertension, hyperlipidemia, diabetes, etc.) who had advanced periodontitis. They found a significant decrease in C-reactive protein at 3 months after the teeth had been extracted. These studies indicate that periodontal therapy could reduce C-reactive protein levels in periodontitis patients with coronary heart disease or cardiovascular risk factors.

As the levels of high-sensitivity C-reactive protein show a dose-dependent response for the risk of coronary disease, the US Centers for Disease Control and Prevention together with the American Heart Association have set high-sensitivity C-reactive protein criteria for cardiovascular disease risk in the adult population: low risk, <1.0 mg/l; average risk, 1.0–3.0 mg/l; high risk, >3.0 mg/l (96). Based on these tertiles of high-sensitivity C-reactive protein, a study showed that periodontal treatment could reduce the relative risk categories (30). In 94 otherwise healthy patients with periodontitis, periodontal therapy resulted in a significant decrease in the number of subjects with average and high C-reactive protein-associated cardiovascular disease risk, with 13 of 94 subjects showing a decrease from high to average risk, 25 showing a decrease from average to low risk, and two showing a decrease from high to low risk. In a recent randomized control study, periodontal therapy was found to reduce high-sensitivity C-reactive protein concentrations below the high level (3 mg/l) and to prevent a drift from average (1–3 mg/l) to high level in non-obese cardiovascular patients (91). These studies indicate that periodontal intervention therapy may decrease the C-reactive protein-associated cardiovascular disease risk.

Fibrinogen

Fibrinogen is the main coagulation protein in plasma, a co-factor for platelet aggregation and an acute-phase reactant. It has been reported that there is an association between elevated plasma fibrinogen levels and coronary heart disease (41, 49). The effects of periodontal treatment on fibrinogen levels are not consistent among the available intervention trials. In some studies, no change in fibrinogen levels were found following periodontal treatment (59, 69, 86, 102). However, in a periodontal intervention study performed in patients with generalized aggressive periodontitis that comprised initial periodontal therapy and antibiotic therapy 8 weeks later, the plasma fibrinogen level had decreased at 6 months after the antibiotic therapy (99). Moreover, a recent study found that non-surgical periodontal therapy was effective in improving periodontal clinical status and reducing the plasma levels of fibrinogen in hypertensive patients with severe periodontitis (122). Taylor et al. (115) also reported a significant decrease in plasma fibrinogen levels 12 weeks after full-mouth tooth extraction in 67 adults.

Cytokines

Many cytokines play a role in the pathogenesis of both coronary heart disease and periodontitis. These include interleukin-1, interleukin-6, interleukin-8, tumor necrosis factor-α, intercellular adhesion molecule-1 (ICAM-1), P-selectin and E-selectin. Some intervention studies (Table 5) have indicated that periodontal therapy can reduce the levels of these pro-inflammory cytokines, and thus periodontal treatment may lower the cardiovascular disease risk.

Interleukin-6

Interleukin-6 is a pleiotropic cytokine, secreted by various cell types, such as fibroblast cells, epithelium cells and monocyte macrophage cells, and its level is increased by factors such as bacterial lipopolysaccharide. Interleukin-6 is involved in promoting coagulation, which may result in the development of atherosclerosis. In a prospective study of 14 916 apparently healthy men, the interleukin-6 levels in 202 men who subsequently had a myocardial infarction were higher than in 202 matched control without myocardial infarction during a 6-year follow-up (1.8 vs. 1.5 pg/ml, $P = 0.002$) (106). This indicates that interleukin-6 levels may be a predictor of risk of future myocardial infarction in apparently healthy men. Severe forms of periodontitis can result in a state of systemic inflammation characterized by elevated serum interleukin-6 (75, 114). A recent study reported that subjects with both coronary artery disease and periodontitis had significantly higher serum interleukin-6 concentrations compared with subjects with coronary artery disease who had no periodontitis ($P < 0.05$) (53).

Table 5. Intervention trials on association between periodontitis and chemokine concentrations

Reference	Study design and periodontal therapy	Number of subjects	Systemic health status	Time points for measurement	Chemokines measured	Measurements of chemokines with statistic significance ($P < 0.05$)	
						Baseline	After therapy
Fokkema et al. (2003) (42)	Case report Extraction of all teeth	1	Healthy	Before and 3, 9, 20 and 32 months after full-mouth extraction	IL-6, TNF-α, IL-8, IL-10, IL-1β, IL-12, MCP-1	IL-8 showed a consistent decrease over time, resulting in a twofold reduction nearly 3 years after baseline MCP-1 showed a twofold reduction compared with baseline (shown graphically, no exact data presented)	
D'Aiuto et al. (2004) (27)	Cohort study Extraction of hopeless teeth, OHI, SRP	94	Healthy	Baseline, 2 and 6 months after completion of treatment	IL-6	1.8 (1.5 IQR) ng/L	1.6
D'Aiuto et al. (2006) (28)	Control group: SRP Test group: SRP + local delivery of minocycline	20/20	Healthy	Baseline, 1, 2 and 6 months after periodontal treatment	IL-6	1.3 ± 0.9; 1.5 ± 1.0 ng/L	0.8 ± 0.6; 1.0 ± 1.9
Elter et al. (2006) (37)	Cohort study Patients with CP: OHI, SRP, periodontal flap surgery where indicated, and extraction of hopeless teeth	22	Healthy	Baseline, 1 month after treatment	IL-6	1.7 (1.5 IQR) pg/ml	1.1 (1.3 IQR)
Forner et al. (2006) (43)	Cohort study Patients with CP: SRP	20	Healthy	Baseline and 8 h after scaling	IL-1β, TNF-α, IL-6, IL-8, IL-10, IL-12	Plasma IL-6 was significantly increased ($P = 0.0049$) and plasma IL-8 was significantly decreased ($P = 0.0192$) 8 h after scaling compared with baseline values	

Table 5. (*Continued*)

Reference	Study design and periodontal therapy	Number of subjects	Systemic health status	Time points for measurement	Chemokines measured	Measurements of chemokines with statistic significance ($P < 0.05$)	
						Baseline	After therapy
Tonetti et al. (2007) (117)	Control group: SRP Test group: SRP + sub-antimicrobial dose minocycline	61/59	Healthy	Before treatment and 1, 7, 30, 60 and 180 days after treatment	IL-6, E-selectin	E-selectin: 19.6 ± 14.0 (test); 20.3 ± 13.6 (control) ng/ml	Levels of soluble E-selectin were lower in the intensive treatment group than in the control treatment group 2 months after therapy (difference 2.7 ng/ml, 95% CI 1.4–8.6, $P = 0.02$) and 6 months after therapy (difference 2.8 ng/ml, 95% CI 1.3–8.4, $P = 0.03$)
Pischon et al. (2007) (99)	Cohort study Patients with AgP: OHI, SRP, systemic antibiotics	21	Healthy	T1: baseline; T2: after OHI; T3: after last SRP; T4: 2 months after SRP; T5: 3 months after antibiotic treatment; T6: 6 months after antibiotic treatment	ICAM-1, VCAM-1, E-selectin, IL-6	E-selectin: 65.95 ng/ml	44.71
Kallio et al. (2008) (64)	Cohort study Patients with CP: OHI, SRP and periodontal flap surgery if indicated	34	Healthy	Baseline and 6 months after periodontal treatment	IL-1β, TNF-α, IL-6	IL-1β: 1.26 ± 1.56 pg/ml	0.86 ± 1.00
Iwamoto et al. (2003) (61)	Cohort study Patients with CP: local antibiotics, supragingival scaling once a week for 1 month	15	Various systemic conditions at high risk for atherosclerosis (IGT, HT, Type 2 DM)	Before and after treatment	TNF-α	2.1 ± 1.6 pg/ml	1.7 ± 1.3

Table 5. (*Continued*)

Reference	Study design and periodontal therapy	Number of subjects	Systemic health status	Time points for measurement	Chemokines measured	Measurements of chemokines with statistic significance ($P < 0.05$)	
						Baseline	After therapy
Lalla et al. (2007) (69)	Cohort study Patients with CP: OHI, SRP, mouth-washes for 2 weeks	10	Diabetes (seven type 1, three type 2)	Baseline and 4 weeks after treatment	IL-1, 2, 4, 5, 6, 7, 8, 10, 12, 13, 15 and17, TNF-α, MCP-1, E-selectin	E-selectin: 27.1 ± 4.5 ng/ml	22.6 ± 3.7
Higashi et al. (2008) (54)	Test group: OHI, SRP and antibiotic therapy; Control group A: without perio-dontitis; Control group B: untreated perio-dontitis	16/20/16	Healthy	Baseline and 24 weeks after periodontal treatment	IL-6	2.3 ± 3.9	1.5 ± 2.2
		17/38/9	Hypertensive			2.8 ± 4.4 ng/l	1.7 ± 2.5
Higashi et al. (2009) (53)	Test group: OHI, SRP and antibiotic therapy; Control group A: without perio-dontitis; Control group B: untreated perio-dontitis	24/53/24	Coronary artery disease	Baseline and 24 weeks after perio-dontal treatment	IL-6	2.6 ± 3.4 ng/l	1.6 ± 2.6

AgP, aggressive periodontitis, IL, interleukin; MCP-1, monocyte chemoattractant protein-1 TNF, tumor necrosis factor. Other abbreviations, see Table 2.

The results of studies on the effect of periodontal intervention therapy on serum interleukin-6 are not consistent (Table 5). Most of the studies took confounding factors such as gender, age, smoking habits and medical history into consideration. Although some studies found no significant differences after treatment (59, 126), others showed that periodontal treatment results in a decrease in interleukin-6 levels (27, 37). In a recent study on coronary artery disease patients with periodontitis, periodontal therapy reduced serum concentrations of interleukin-6 from 2.6 ± 3.4 to 1.6 ± 2.6 ng/l ($P < 0.05$) at 6 months after therapy (53). We obtained similar findings in an unpublished study in which 45 periodontitis patients with coronary heart disease received mechanical periodontal treatment and 41 control patients did not receive periodontal therapy. The serum interleukin-6 levels in periodontal treatment group decreased significantly from 39.1 ± 22.5 to 30.9 ± 19.9 ng/l at 3 months after periodontal treatment, but no significant change was found in the control group at 3 months (from 36.9 ± 23.6 to 42.8 ± 24.3 ng/l).

Tumor necrosis factor-α

Tumor necrosis factor-α is a cytokine with a wide range of humoral and cellular immune effects relating to inflammation, and is involved in the initiation and development of coronary artery disease (25, 38). Tumor necrosis factor-α levels are increased in patients with periodontitis (48). The influence of periodontal treatment on circulating tumor necrosis factor-α levels is not clear, with some studies reporting no effect following periodontal intervention (42, 43, 59, 69, 126), and others reporting significant decreases in tumor necrosis factor-α levels after periodontal therapy (60, 61), even though all of the studies considered confounding factors and the subjects in the various groups were well matched.

Adhesion molecules

E-selectin

E-selectin is a glycoprotein that is expressed in activated vascular endothelium and plays a role in initiation of the inflammatory process (71). The circulating level of E-selectin is used as a surrogate marker of endothelial function (15). High levels of E-selectin may predict the development of cardiovascular disease.

The results of periodontal intervention treatment on the plasma levels of soluble E-selectin in various studies have been consistent. In systemically healthy subjects with periodontitis, periodontal treatment resulted in a short increase in soluble E-selectin in the plasma on day 1 (29, 117). One month after periodontal therapy, the levels of E-selectin were significantly reduced compared with baseline (29). Two and 6 months after intensive periodontal treatment, including oral hygiene instruction, scaling and root planing, and local application of antibiotics, the level of E-selectin remained significantly lower than in the control group who received oral hygiene instruction, supragingival scaling and polishing only (117). In aggressive periodontitis patients, mechanical periodontal therapy resulted in a significant reduction in plasma E-selectin levels at 2 weeks and 2 months after treatment. Antibiotic treatment did not further decrease the E-selectin levels, but the low E-selectin levels were maintained throughout the following 6 months (99). A pilot study reported the differences in E-selectin levels after periodontal treatment in ten diabetes patients with moderate to severe periodontitis (69). Four weeks after therapy, the E-selectin levels had significantly decreased by 16.6%. These results indicate that periodontal intervention therapy has a beneficial influence on E-selectin levels, and therefore could assist in improvement of endothelial dysfunction.

Intercellular adhesion molecule-1

Intercellular adhesion molecule-1 (ICAM-1) belongs to the immunoglobulin superfamily and mediates white blood cell adherence to blood vessel endothelium cells (51). It has been reported that subjects with hypercholesterolemia and hypertriglyceridemia have significantly increased concentrations of soluble ICAM-1 (50). Furthermore, expression of ICAM-1 is enhanced in the periodontal tissue in patients with periodontitis (84). Few studies have assessed the influence of periodontal intervention on soluble ICAM-1 levels, although at least one study has reported that the concentration of soluble E-selectin decreases significantly after periodontal therapy, but the levels of soluble ICAM-1 and vascular cell adhesion molecule-1 levels remain unaffected (99). Therefore, the modulation of soluble ICAM-1 levels by periodontal therapy is not clear, and more studies are required.

White blood cell count

It is well accepted that inflammation is one of the causal risk factors for cardiovascular disease. As a direct marker of inflammation, the white blood cell count is associated in a dose–response manner with cardiovascular disease.

It is well known that infections lead to increased leukocyte counts. Periodontal disease is a chronic infection and may be related to cardiovascular disease through infection-related mediators and hyper-reactivity of white blood cells. Several studies have reported that leukocyte counts in periodontitis patients are significantly increased compared with healthy controls (44, 45, 75, 113).

Even though some studies did not find statistically significant differences in white blood cell count before and after treatment (23, 111), others reported that periodontal intervention therapy has an effect in decreasing the leukocyte count (22, 42) (Table 6). For example, Christan et al. (22) studied the effect of periodontal therapy in 27 otherwise healthy subjects with severe periodontitis, and found that there was a significant decrease in total white blood cell count and neutrophil counts after periodontal therapy. If local antibiotics were used as an adjunct to periodontal treatment, greater reductions in white blood cell count were obtained (28, 117). In a 43-year-old male with generalized terminal adult periodontitis, the white blood cell count significantly decreased over the 32 months after all his teeth were extracted (42). As the white blood cell count directly indicates the amount of systemic inflammation, this periodontal treatment, which resulted in a reduction of white blood cell count, may have had an effect in lowering the risk of cardiovascular disease.

Influence of periodontal intervention on haemostatic factors

Numerous studies have found that increased levels of certain haemostatic factors such as fibrinogen, von Willebrand factor and tissue plasminogen activator play a role in the development of cardiovascular disease and may be associated with an increased risk of coronary events (116, 123). Haemostatic factors are also known to be associated with periodontitis, and may be possible intermediate factors linking periodontal disease to an elevated risk of cardiovascular disease (13, 68, 82, 85, 108, 110, 124, 125). Several clinical studies have investigated the influence of periodontal intervention on haemostatic factors such as plasminogen activator inhibitor antigen (PAI-1) and von Willebrand factor, and are discussed below.

Tissue-type plasminogen activator and plasminogen activator inhibitor-1

Tissue-type plasminogen activator is released from endothelial cells, and is the major physiological activator of plasminogen. Circulating tissue-type plasminogen activator is rapidly inactivated by its inhibitor plasminogen activator inhibitor-1 (PAI-1), and plasma levels of PAI-1 are related to risk for coronary heart disease. Studies on the relationship between tissue-type plasminogen activator and periodontitis are very limited. However, one study has shown that, after multiple logistic regression and adjustment for all risk factors for coronary heart disease, significant relationships exist between clinical periodontal parameters and PAI-1 levels (85). In an intervention study, Taylor et al. (115) reported a significant decrease in levels of PAI-1 at 12 weeks after full-mouth tooth extraction. However, no improvement in PAI-1 levels was reported in patients with moderate to severe periodontitis and diabetes 4 weeks after periodontal therapy (69). In another periodontal intervention study, periodontal therapy resulted in an overall reduction of systemic inflammation, including PAI-1 levels, but the responses were highly variable across subjects and were mostly not sustainable (11).

Tonetti et al. (117) found a sharp increase in the levels of von Willebrand factor and PAI-1 at 24 h after intensive periodontal therapy compared with a control treatment group. However, 6 months after periodontal intervention, the levels of these haemostatic factors had decreased, and showed no significant change compared to baseline and control treatment group levels. This may indicate short-term endothelial dysfunction after periodontal intervention, but it is not clear whether there is a relationship between periodontitis and alteration in levels of tissue-type plasminogen activator or PAI-1.

In general, the levels of plasma haemostatic factors appear to be related to endothelial injury, endothelial cell activation, pro-thrombotic state, inflammation, fibrolysis and plaque rupture, all of which contribute to the pathogenesis of coronary heart disease and the incidence of cardiovascular and cerebrovascular events. However, the plasma levels of haemostatic factors are regulated and influenced by a number of variables, such as genetics, smoking, blood lipid levels, age, inflammation and glucose. Accordingly, some studies have noted that certain haemostatic factors are not an independent predictor of cardiovascular disease (31, 80), and there may be many potential determinants influencing the dynamics of their responses to periodontal intervention. Hence,

Table 6. Intervention trials on association between periodontitis and number of white blood cell count count

Reference	Study design and periodontal therapy	Number of subjects	Systemic health status	Time point for measurement	White blood cell count (10^3 / µl) ($P < 0.05$)	
					Baseline value for each group	After therapy
Christan et al. 2002(22)	Cohort study Patients with CP: OHI, supragingival scaling, SRP, maintenance therapy	27	Healthy	Baseline and 3 months after completion of periodontal treatment	7.2 Neutrophils: 4.41	5.7 3.33
Fokkema et al. 2003 (42)	Cohort study Extraction of all teeth	1	Healthy	Before and 3, 9, 20 and 32 months after full-mouth extraction	4.42 Neutrophils: 2.86	3.80 2.31
D'Aiuto et al. 2006 (28)	Control group: SRP Test group: SRP + local delivery of minocycline	20 / 20	Healthy	Baseline, 1, 2 and 6 months after periodontal treatment	7.3 ± 2.2; 6.6 ± 1.6	6.5 ± 2.0; 6.0 ± 1.8
Tonetti et al. 2007(117)	Control group: supra-gingival scaling Test group: SRP + sub-antimicrobial dose minocycline	61 / 59	Healthy	Before treatment and 1, 7, 30, 60 and 180 days after treatment	6.4 ± 1.6 7.1 ± 2.0 (control)	The neutrophil count was lower after treatment compared to the control group
Lalla et al. 2007 (69)	Cohort study Patients with CP: OHI, SRP, mouthwashes for 2 weeks	10	Diabetes (seven type 1, three type 2)	Baseline and 4 weeks after treatment	$CD14^+$ mononuclear cells (%): 17.0 ± 6.1	9.0 ± 1.2

additional research is required to assess the determinants of the unexplained variance.

Influence of periodontal intervention on endothelial dysfunction

Endothelial dysfunction is a fundamental step in the development of atherosclerosis, and can be measured by several methods, including flow-mediated dilatation of the brachial artery. Endothelial dysfunction as determined by measurement of brachial flow-mediated dilatation is considered to be a good predictor of cardiovascular outcomes (107).

Periodontal disease is associated with endothelial dysfunction as measured by brachial flow-mediated dilatation. Endothelial function has been reported to be significantly lower in patients with periodontitis than in control subjects (2, 17, 54, 81, 111). In addition, endothelial dysfunction in hypertensive patients with periodontitis is more severe compared to hypertensive patients without periodontitis (54). Recently, endothelial function was evaluated in healthy and periodontitis patients with coronary artery disease (53). The results showed that endothelial function was significantly lower in the periodontitis group with coronary artery disease than in the non-periodontitis group with coronary artery disease. These results suggest that periodontitis is a contributor to endothelial dysfunction, and hence could increase the risk of cardiovascular disease.

The influence of periodontal therapy on endothelial dysfunction, as measured by flow-mediated dilation of the brachial artery, has been studied. Table 7 provides a summary of these studies. An early study showed that, for systemically healthy subjects with periodontitis, initial periodontal therapy improved the impaired endothelial function at 6 weeks after non-surgical periodontal therapy without using antimicrobial agents (81). In two pilot studies, non-surgical periodontal therapy, including use of antibiotics, led to a significant improvement of endothelial dysfunction in severe periodontitis patients 3 months after treatment (17, 111). Changes in endothelial function during a 1-month period without periodontal treatment and a 1-month period after periodontal therapy were observed in 22 patients with moderate to severe periodontitis (37). Periodontal therapy included scaling and root planing, extraction of hopeless teeth and periodontal flap surgery where indicated. The results showed no significant changes during the month without treatment, but significant improvement at 1 month after periodontal treatment. A randomized control trial has provided strong evidence for the effect of periodontal intervention on endothelial dysfunction (117). Patients with severe periodontitis were randomized to intensive periodontal therapy (61 patients) or control treatment (community-based periodontal care) (59 patients). Intensive periodontal therapy included oral hygiene instruction, scaling and root planing, local delivery of minocycline to periodontal pockets and extraction of hopeless teeth. The control treatment included oral hygiene instruction and supragingival ultrasonic debridement. Fifty-eight patients in the intensive treatment group and 56 patients in control treatment group completed the study. The control treatment group showed no significant changes in flow-mediated dilatation over the 6-month observation period. The intensive periodontal therapy group showed worsening of flow-mediated dilatation 24 h after treatment, but significant improvement of flow-mediated dilation at 2 and 6 months compared to the control treatment group. The improvement of endothelial dysfunction correlated with the reduction in the number of periodontal pockets and the reduction of bleeding on probing. In this trial, possible confounding factors including age, sex, race, family history of cardiovascular disease, diet, medication regimen, smoking status, lipid levels, body mass index, blood glucose levels and blood pressure were considered and compared between two groups. Apart from systolic blood pressure, which was significantly higher in patients in the test group 24 h after treatment, no significant difference was found for the other factors between the test and control groups. Another small 6-month randomized control trial showed similar results (54). Periodontitis patients without cardiovascular risk factors were randomly divided into a periodontitis treatment group (16 patients) and an untreated group (16 patients). All patients in both groups were non-smokers. Periodontal treatment included oral hygiene instruction, subgingival scaling and root planing and antibiotics use. The results showed that periodontal therapy increased acetylcholine-induced vasodilation, indicating that the endothelial dysfunction had improved. These pilot studies and randomized controlled trials studies have provided consistent evidence to indicate that periodontal therapy leads to an improvement of endothelial dysfunction in systemically healthy patients with periodontitis.

Recently, two studies have reported the effects of periodontal therapy on the endothelial function in

Table 7. Studies assessing the effect of periodontal therapy on endothelial function

Reference	Study design	Measurement of endothelial function	Results	Conclusions
Mercanoglu et al. (2004) (81)	28 chronic periodontitis patients without systemic disease (45.5 ± 8.6 years) 26 healthy controls (43.7 ± 6.8 years) Periodontal therapy: OHI + SRP within 4 weeks Control group only given OHI Data obtained before and 6 weeks after periodontal therapy	Endothelium-dependent flow-mediated dilatation of the brachial artery (EDD) Endothelium-independent flow-mediated dilatation (EID)	Both EDD and EID improved significantly in periodontal patients after periodontal therapy (8.4 ± 4.0% to 17.7 ± 5.7%, $P < 0.0001$; 13.3 ± 6.3% to 24.9 ± 7.3%, $P < 0.0001$) The changes in EDD and EID in controls were insignificant.	Endothelial functions in patients with chronic periodontitis were impaired. Initial periodontal therapy improved their endothelial functions.
Seinost et al. (2005) (111)	30 severe periodontitis patients without systemic disease (25–50 years) Periodontal therapy: OHI + SRP in two sessions + 0.1% chlorhexidine gluconate mouth washes for 14 days + systemic antimicrobial therapy for 7 days (amoxicillin plus clavulanic acid and metronidazole Data obtained before and 12 weeks after periodontal therapy	Endothelium-dependent flow-mediated dilatation of the brachial artery (FMD) Endothelium-independent nitroglycerin-associated dilation (NAD)	Successful periodontal treatment improved the FMD significantly from 6.1% ± 4.4% to 9.8% ± 5.7% ($P = 0.003$). NAD did not differ between the study groups at baseline or after periodontal therapy.	Treatment of severe periodontitis reverses endothelial dysfunction.
Elter et al. (2006) (37)	Single-masked pilot trial: 22 moderate to severe chronic periodontitis patients (otherwise healthy) (age > 30 years, mean 42 ± 6 years) Periodontal therapy: SRP + extraction of hopeless teeth + periodontal flap surgery where indicated + whole-mouth disinfection, completed over one or two visits less than 2 weeks apart Data obtained at baseline (baseline 1), after 1 month without treatment (baseline 2) and 1 month after periodontal therapy	Flow-mediated (endothelium-dependent) dilation of the brachial artery (FMD) Nitroglycerin-mediated (endothelium-independent) dilation of the brachial artery (NTG-MD)	No significant changes in FMD or NTG-MD between baseline measurements 1 and 2 (FMD: 8.9 ± 4.7% to 8.2 ± 5.0%; NTG-MD: 19.7 ± 7.7% to 20.3 ± 10.6%) Mean flow-mediated dilation improved after periodontal therapy (FMD: 8.6 ± 4.7% to 10.2 ± 3.9, $P = 0.034$) Nitroglycerin-mediated dilation remained unchanged (NTG-MD: 19.8 ± 8.6% to 21.3 ± 8.0%, $P = 0.365$)	Improvement in endothelial function may be possible through near-elimination of chronic oral infection.

Table 7. (*Continued*)

Reference	Study design	Measurement of endothelial function	Results	Conclusions
Blum et al. (2007) (17)	22 severe periodontitis patients without systemic disorders(40 ± 5 years) 13 patients came for a second visit after 3 months of treatment Periodontal therapy: OHI + SRP + antibiotics (amoxicillin 500 mg + metronidazole 250 mg, tid) Healthy controls: 10 age-matched volunteers Data obtained at baseline and 3 months after periodontal therapy	Endothelium-dependent dilation of the brachial artery (FMD) Endothelium-independent dilation of the brachial artery (FID)	At baseline: periodontitis patients group had lower FMD than the control group (FMD: 4.12 ± 3.96% versus 16.60 ± 7.86%, $P = 0.0000$) Three months after treatment, endothelial function had improved in periodontitis patients (FMD: 4.12 ± 3.96% to 11.12 ± 7.22%, $P = 0.007$) No difference in FID was found after treatment (FID: 20.97 ± 10.66% to 17.94 ± 6.23%, $P = 0.448$)	Periodontitis may be an cause of endothelial dysfunction and cardiovascular events. Treating periodontitis can improve endothelial function and may be an important preventive tool for cardiovascular disease.
D'Aiuto et al. (2007) (29)	55 systemically healthy severe periodontitis patients (age range 30–65 years) Periodontal therapy: mechanical instrumentation of the whole dentition (within 6 h) Data obtained before and 1, 7 and 30 days after periodontal therapy	Biomarkers for endothelial cell activation: soluble E-selectin and von Willebrand factor antigen	Soluble E-selectin plasma concentrations at day 1 after periodontal therapy showed a 10% increase, but were significantly reduced 30 days after periodontal therapy ($P < 0.05$) von Willebrand factor antigen showed a 30% increase at day 1 and day 30 after periodontal therapy	Periodontal therapy resulted in a mild acute increase plasma soluble E-selectin levels and followed by a long-term significant reduction. Periodontal therapy produced an increase in the levels of von Willebrand factor antigen.

Table 7. (*Continued*)

Reference	Study design	Measurement of endothelial function	Results	Conclusions
Tonetti et al. (2007) (117)	RCT study: 120 patients with severe periodontitis randomly assigned to community-based periodontal care (n = 59) or intensive periodontal treatment (n = 61) Periodontal therapy: community-based periodontal care: OHI + supragingival scaling + polishing; intensive periodontal treatment: OHI + SRP + extraction of teeth that could not be saved + local antibiotics (minocycline) Data obtained before and 1, 7, 60 and 180 days after periodontal therapy 58 patients in the intensive treatment group and 56 patients in the control treatment group completed the study	Endothelium-dependent dilation of the brachial artery (FMD) Endothelium-independent dilation (nitroglycerin-mediated dilation) of the brachial artery (EID) Markers of endothelial activation: soluble E-selectin (s-Es) and von Willebrand factor	FMD was lower in the intensive periodontal treatment group than in the control group at 24 h after periodontal therapy (absolute difference 1.4%; 95% CI 0.5–2.3; $P = 0.002$). At 2 and 6 months after therapy, FMD was greater in the intensive periodontal treatment group than in the control group (60 days: absolute difference 0.9%, 95% CI 0.1–1.7, $P = 0.02$; 180 days: absolute difference 2.0%, 95% CI 1.2–2.8, $P < 0.001$) The degree of improvement was correlated with reduction in the number of periodontal lesions and with a reduction in scores for full-mouth bleeding ($r = 0.30$ and 0.29 by Spearman rank correlation, $P = 0.002$ and 0.003, respectively). A significant effect of time was found for nitroglycerin-mediated dilatation, but no interaction between treatment and time was found. For soluble E-selectin, values were higher in the intensive treatment group than in the control treatment group at 24 h after therapy (difference 1.8 ng/ml, 95% CI 1.1–2.8, $P = 0.02$) Values at 2 and 6 months after therapy were lower in the intensive treatment group than in the control treatment group (2 months: difference 2.7 ng/ml, 95% CI 1.4-8.6, $P = 0.02$; 6 months: difference 2.8 ng/ml, 95% CI 1.3-8.4, $P = 0.03$)	Intensive periodontal therapy resulted in acute, short-term endothelial dysfunction, but improvement of endothelial function at 6 months after therapy.

Table 7. (*Continued*)

Reference	Study design	Measurement of endothelial function	Results	Conclusions
Higashi et al. (2008) (54)	32 patients with periodontitis without cardiovascular risk factors were randomly divided into a periodontal treatment group (n = 16, mean age 25 ± 3 years) and an untreated group (n = 16, mean age 25 ± 4 years) 26 hypertensive patients with periodontitis were divided into a periodontal treatment group (n = 17, mean age 53 ± 14 years) and an untreated group (n = 9, mean age 55 ± 11 years) Periodontal treatment: OHI + SRP + antibiotics (4–7 days) Data obtained before and 24 weeks after periodontal therapy	FBF to Ach FBF to SNP FBF in the presence of L-NMMA	FBF to Ach increased significantly after 24 weeks of periodontal therapy in periodontitis patients without cardiovascular risk factors and in periodontitis patients with hypertension. No significant difference between baseline and 24 weeks was found in the two untreated groups for patients without cardiovascular risk factors and those with hypertension. For FBF to SNP, the differences between the beginning and the end of the 24-week study period were similar in both periodontal therapy groups and untreated groups for patients without cardiovascular risk factors and patients with hypertension. After administration of L-NMMA, FBF to Ach was similar before and after treatment in both patients without cardiovascular risk factors and those with hypertension.	Periodontal therapy augmented acetylcholine-induced vasodilation in periodontitis patients with and without hypertension. L-NMMA, an NO synthase inhibitor, completely abolished the periodontal therapy-induced augmentation of the FBF response to Ach in both patients without cardiovascular risk factors and patients with hypertension.

Table 7. (*Continued*)

Reference	Study design	Measurement of endothelial function	Results	Conclusions
Higashi et al. (2009) (53)	Randomized controlled trial: 48 periodontitis patients with coronary artery disease were assigned to periodontal therapy (n = 24, mean age 64 ± 14 years) or no periodontal therapy (n = 24, mean age 63 ± 13 years) Periodontal treatment: OHI + SRP + antibiotics (4–7 days) Data obtained before and 24 weeks after periodontal therapy	FBF to Ach FBF to SNP FBF in the presence of L-NMMA	FBF to Ach increased significantly after 24 weeks of periodontal therapy (from 14.7 ± 5.2 to 20.1 ± 6.1 ml/min per 100 ml) No significant differences was seen in the untreated group. For FBF to SNP, the differences between the beginning and the end of the 24-week study period were similar in both the periodontal therapy group and the untreated group After administration of L-NMMA, FBF to Ach was similar before and after periodontal treatment	Periodontal therapy augmented acetylcholine-induced vasodilation in periodontitis patients with coronary artery disease. L-NMMA completely abolished the periodontal therapy-induced augmentation of FBF response to Ach in patients with coronary artery disease

Ach, acetylcholine; CI, confidence interval; EDD, endothelium-dependent dilatation; EID, endothelium independent dilatation; FBF, forearm blood flow; FMD, flow-mediated dilatatioin; L-NMMA, N^G-monomethyl–L-arginine; NAD, nitroglycerin-associated dilation; NTG-MD, nitroglycerin-mediated dilation; RCT, randomized controlled trial; SNP; sodium nitroprusside.

periodontitis patients with hypertension or coronary artery disease (53, 54). Periodontitis patients with hypertension were divided into a periodontitis treatment group (17 patients) and an untreated group (9 patients). There was no significant difference in body mass index, blood pressure, total cholesterol, triglyceride, HDL and LDL cholesterol or glucose between the groups. The endothelial function was evaluated in terms of forearm blood flow responses to acetylcholine. The untreated group showed no significant change between baseline and 3 months follow-up. However, periodontal treatment group showed that the endothelial dysfunction improved significantly (54). Similar results were found in a study of periodontitis patients with coronary artery disease. Periodontitis patients with coronary artery disease were randomly assigned into a periodontal treatment group (24 patients) and a control group (24 patients). They were all non-smokers. The patients in both groups had similar clinical characteristics, including age, gender, body mass index, blood pressure, cholesterol, triglyceride, HDL and LDL cholesterol, glucose and medical history. The endothelial function in the treatment group increased significantly 3 months after periodontal therapy, but did not change significantly in the untreated group (53). It was concluded that periodontal therapy improved endothelial dysfunction not only in periodontitis patients with hypertension but also in periodontitis patients with coronary artery disease. These findings need to be confirmed in large-scale clinical studies.

One possible mechanism for periodontitis-induced endothelial dysfunction and improvement in endothelial dysfunction following periodontal therapy has been studied (53, 54). After administration of a nitric oxide synthase inhibitor (N^G-monomethyl-L-arginine) the difference in forearm blood flow responses to acetylcholine between periodontitis patients and normal controls disappeared. The enhancement of endothelial function by periodontal treatment was also inhibited by the NO synthase inhibitor. This indicates that the increase of NO production after periodontal treatment may play an important role in the relationship between enhanced endothelial function and periodontal therapy.

Based on current evidence, periodontal therapy can improve endothelial dysfunction in periodontitis patients whether they are systemically healthy or have hypertension. This further confirms the causal association between periodontitis and endothelial dysfunction. As endothelial dysfunction is associated with an adverse prognosis for atherosclerosis and cardiovascular disease, periodontal intervention therapy may bring benefits to patients with periodontitis by improving endothelial dysfunction and thus reducing the risk of cardiovascular disease. However, this requires further study.

Influence of periodontal therapy on intima–media thickness of the arterial wall

The intima–media thickness of the arterial wall is a parameter of atherosclerosis. The carotid intima–media thickness is highly correlated with coronary artery disease and cerebral disease.

In a pilot study, no significant difference in brachial artery intima–media thickness was noted before and 3 months after non-surgical periodontal treatment that included systemic antimicrobial therapy (111). However, more recently, a reduction in the carotid intima–media thickness was observed after periodontal treatment (98). In this longitudinal study, 35 otherwise healthy subjects with mild to moderate periodontitis were enrolled. Non-surgical debridement was performed and completed within 4 weeks. Echo-Doppler cardiography of the carotid artery was evaluated before and 1, 6 and 12 months after the periodontal treatment. The results showed that the carotid intima–media thickness was significantly reduced at 6 and 12 months after treatment, and the decrease in the carotid intima–media thickness was detected at multiple sites along the carotid axis: at the carotid bifurcation and at 1 and 2 cm from the bifurcation. This indicates a beneficial effect of periodontal treatment on the carotid intima–media thickness.

Influence of periodontal treatment on immunophenotypic expression and gene expression of monocytes

Many studies have shown that mononuclear cells play an important role in atherosclerotic plaque formation. Monocytes/macrophages and circulating CD4 T cells infiltrate the arterial wall, engulf the proatherogenic-modified forms of low density lipoprotein, and become foam cells. During these events, the phenotypes of the monocytes/macrophages change. In addition, many cytokines are involved, and circulating monocytes and lymphocytes become important sources of these cytokines (12, 19, 73). The mechanisms involved in the association of periodontitis and cardiovascular disease are still under investigation. Recent studies have focused on the changes in immunophenotypic expression and gene expression in circulating monocytes and lymphocytes in periodontal intervention trials, because these cells are likely to be determinants of atherosclerosis.

Papapanou et al. (94) evaluated the effect of periodontal treatment on gene expression in peripheral blood monocytes. Fasting blood samples were collected from 15 patients with moderate to severe periodontitis (without systemic diseases and a history of regular antibiotic use or smoking) at four time points: 1 week before periodontal treatment, at treatment initiation (baseline), and at 6 and 10 weeks after treatment initiation. The gene expression profiles in peripheral blood monocytes were analyzed at each time point. The results showed a substantial improvement in clinical periodontal status after periodontal treatment, and reduction in the levels of several periodontal pathogens. Seven genes relevant to innate immunity, apoptosis and cell signaling showed substantially reduced expression in approximately one-third of the patients, including those encoding CD36 antigen (thrombospondin receptor), fibrinogen-like 2, chondroitin sulfate proteoglycan 2 (versican), Toll-like receptor 8, Toll-like receptor 2, integrin αM chain (complement component 3 receptor 3 subunit), Toll-like receptor 1. These data indicate that monocyte gene expression is altered by periodontal therapy, in a manner consistent with a systemic anti-inflammatory effect.

Two studies observed phenotypic functional changes in monocytes after periodontal intervention treatment. Lalla et al. (69) assessed the effects of anti-infective periodontal treatment in patients with diabetes, and observed changes in the immunophenotypic expression of monocytes and lymphocytes. The results showed that the number of $CD14^+$ blood monocytes decreased by 47% ($P < 0.05$), and the percentage of macrophages spontaneously releasing tumor necrosis factor-α decreased by 78% ($P < 0.05$). There were no significant differences in the mean surface expression of CD11a, CD11b, CD18, CD49d or CD36 in monocytes after treatment, and neither were there any changes in the percentages of lymphocytes that stained positively for CD3, CD4, CD8 and CD25. The CD4/CD8 ratio was unchanged. In another study, Piconi et al. (98) investigated changes in lymphocyte differentiation following non-surgical debridement of 35 otherwise healthy patients with mild to moderate periodontitis. Whole blood samples were taken at baseline and 1, 6 and 12 months after the periodontal treatment, and lymphocyte subsets were evaluated. These immunophenotypic analyses showed that the proportion of $CD4^+HLA\text{-}DR^+$ T cells (activated T cells) significantly decreased 6 months after periodontal treatment ($P = 0.029$). $CD44^+$ and $CD49d^+$ expression by $CD4^+$ T cells was reduced from its baseline level. It was also noted that the proportion of Toll-like receptor-expressing CD14 cells and $CD14^+$ $CD36^+$ monocytes significantly decreased following periodontal treatment, consistent with an animal study (70). In Piconi's study, to minimize the impact of confounding factors, patients with established cardiovascular risk factors (e.g. hypercholesterolemia, diabetes, obesity, hypertension, history of stroke or heart attack) were excluded from the study in order to reduce the impact of confounding factors. These findings suggest that periodontal treatment can modulate the systemic inflammatory process, influence the differentiation of inflammatory cells, and decrease the secretion of cytokines involved in formation of foam cells. In addition, these studies have shown that periodontal therapy can influence the immunophenotypic expression and gene expression of monocytes, which is important in reducing the risk of atherosclerosis.

Conclusion

According to the available data, periodontal intervention therapy has a positive impact on established risk factors for cardiovascular disease. The interventional studies have strengthened the evidence for an association between periodontitis and cardiovascular disease and indicate a causal link. Nevertheless, further large-scale, better-designed studies with longer follow-up and clinical endpoint as observation parameters are required.

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