Japanese Dental Science Review (2009) **45**, 98—108

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/jdsr

REVIEW ARTICLE

Periodontitis and cardiovascular diseases: The link and relevant mechanisms

Yuichi Izumi [a,b,*], Toshiyuki Nagasawa [c], Makoto Umeda [a], Hiroaki Kobayashi [a], Yasuo Takeuchi [a], Reiko Yashiro [a], Doosadee Hormdee [d], Tomonari Suda [a], Yuka Ushida [a], Nawarat Wara-aswapati [d]

[a] *Section of Periodontology, Department of Hard Tissue Engineering, Graduate School, Tokyo Medical and Dental University, Tokyo, Japan*
[b] *Global Center of Excellence (GCOE) Program, International Research Center for Molecular Science in Tooth and Bone Diseases, Tokyo Medical and Dental University, Tokyo, Japan*
[c] *Department of Periodontology and Endodontology, Division of Oral Maxiollofacial Rehabilitation, Health Sciences University of Hokkaido, Hokkaido, Japan*
[d] *Department of Periodontology, Faculty of Dentistry, Khon Kaen University, Khon Kaen, Thailand*

Received 10 March 2009; received in revised form 25 May 2009; accepted 1 June 2009

KEYWORDS
Periodontitis;
Cardiovascular diseases;
Atherosclerosis;
Buerger's disease;
Periodontal treatment

Summary This paper reviews the association between periodontitis and CVD. In addition, the potential mechanisms of any association between periodontitis and CVD as well as the effects of periodontal treatment on CVD are herein discussed. Among the studies carried out by this group and others on coronary artery diseases, peripheral arterial diseases, abdominal aortic aneurysm, and Buerger's disease, periodontopathic bacteria were frequently detected in the diseased blood vessels, thus suggesting an association between periodontitis and CVD. The potential mechanisms of the association between periodontitis and CVD are not fully elucidated. However, inflammation and some autoimmune mechanisms, including molecular mimicry between the periodontopathic bacteria and host molecules, are suggested. The effects of periodontal treatment on CVD might thus vary among the different treatment modalities, and full-mouth mechanical debridement might induce strong transient systemic inflammatory responses in comparison to the quadrant-wise mechanical debridement.

Contents

1. Introduction 99
2. Effects of periodontitis on atherosclerosis 99

* Corresponding author at: Section of Periodontology, Department of Hard Tissue Engineering, Graduate School, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, 113-8549 Tokyo, Japan. Tel.: +81 3 5803 5486; fax: +81 3 5803 5486.
E-mail address: y-izumi.peri@tmd.ac.jp (Y. Izumi).

1882-7616/$ — see front matter
doi:10.1016/j.jdsr.2009.06.001

2.1. Coronary artery disease . . . 99
2.2. Peripheral vascular disease . . . 100
2.3. Abdominal aortic aneurism . . . 101
2.4. Buerger's disease . . . 102
3. Potential mechanisms of the association between periodontitis and CVD . . . 102
4. Effects of periodontal treatment on cardiovascular diseases . . . 104
5. Conclusion . . . 105
Acknowledgement . . . 105
References . . . 105

1. Introduction

Cardiovascular disease (CVD) is a class of diseases that affect the heart and blood vessels. Globally, CVD is the number one cause of death and is estimated to remain so. The WHO report released in 2007 (Fact sheet No. 317, February 2007) reported an estimated 17.5 million people died from CVD in 2005, representing 30% of all global deaths.

Accumulating evidence shows that inflammation played a central role in the pathogenesis of CVD [1,2]. Periodontitis is an inflammatory disease caused by gram-negative periodontopathic bacteria which can induce the production of host inflammatory mediators, eventually leading to the breakdown of tooth-supporting tissues [3,4]. Recent studies and meta-analyses have demonstrated a modest but statistically significant association between CVD and periodontitis (odds ratios: 1.1—2.2) [5—11]. In addition, it has been suggested that periodontitis may contribute to CVD and stroke [11,12].

Periodontal pathogens have been detected in atherosclerotic plaques in humans and animal models, suggesting that periodontal infections may result in bacteremias and enhance atherosclerotic plaque formation [13—15]. A number of inflammatory cytokines, which have been reported to be associated with periodontitis, are also involved in atherothrombogenesis [16,17]. Furthermore, patients with periodontal disease share many of the same risk factors as patients with CVD including age, gender (predominantly male), lower socioeconomic status, stress, and smoking [18]. This suggests that periodontal disease and CVD may share common etiological pathways and that the association between these two diseases is plausible.

This paper reviews the association between periodontitis and CVD with a focus on studies carried out by this group on coronary artery diseases, peripheral arterial diseases, abdominal aortic aneurysm, and Buerger's disease. In addition, potential mechanisms of the association between periodontitis and CVD as well as the effects of periodontal treatment on CVD are discussed.

2. Effects of periodontitis on atherosclerosis

2.1. Coronary artery disease

Coronary arteries deliver oxygen-rich blood to the myocardium. In general, there are two main coronary arteries, which are the right coronary artery and the left coronary artery. These arteries run on the surface of the heart and are capable of auto-regulation to maintain coronary blood flow at the levels appropriate to the needs of the heart muscles. Coronary artery disease (CAD), which is also called coronary heart disease (CHD), is the end result of the accumulation of atheromatous plaques within the walls of the arteries.

Myocardial infarction occurs when the atheromatous process prevents blood flow through the coronary artery. It was previously thought that progressive luminal narrowing from continued growth of smooth-muscle cells in the plaque was the main cause of infarction. Angiographic studies have, however, identified culprit lesions that do not cause marked stenosis, and it is now evident that the activation of plaque rather than stenosis precipitates in the subsequent ischemia and infarction. Coronary spasm may be involved to some extent, but most cases of infarction are due to the formation of an occluding thrombus on the surface of the plaque.

There are two major causes of coronary thrombosis: plaque rupture and endothelial erosion. Plaque rupture, which is detectable in 60—70% of cases, is dangerous because it exposes pro-thrombotic material from the core of the plaque-phospholipids, tissue factor, and platelet-adhesive matrix molecules to the blood. Ruptures preferentially occur where the fibrous cap is thin and partly destroyed. Activated immune cells are abundant at these sites. They produce numerous inflammatory molecules and proteolytic enzymes that can weaken the cap and activated cells in the core and transform the stable plaque into a vulnerable, unstable structure which can rupture, induce a thrombus, and also cause acute coronary syndrome.

Several studies have linked infections to atherosclerosis and CAD. The conditions or infectious agents most frequently studied are *Chlamydia pneumoniae*, cytomegarovirus (CMV), herpes simplex virus (HSV), *Helicobacter pylori* and periodontitis [19].

Tooth loss may be associated with an increased risk of CAD and stroke [20,21]. After adjusting for potential confounders, periodontitis is associated with an increase of 25% in CAD risk and an increased risk of up to 70% among men less than 50 years of age [22]. There does appear to be increasing evidence of a relationship between dental health and CAD, especially in men ranging from 40 to 50 years of age.

In an animal study [23], recurrent *Porphyromonas gingivalis* (*P. gingivalis*) bacteremia induces coronary lesions consistent with atherosclerosis and accelerates coronary atherosclerosis. Sakurai et al. [24] showed the presence of *Aggregatibacter actinomycetemcomitans* (*A. actinomycetemcomitans*) to be higher in patients with acute coronary syndrome (ACS) than in those of chronic CHD (Table 1). In addition, ACS patients showed significantly higher serum IgG titers against *A. actinomycetemcomitans* in comparison to chronic CHD (Fig. 1). These results suggest the possibility of a

Table 1 Presence of periodontopathic bacteria in oral (saliva and/or subgingival plaque) and blood samples in coronary heart disease patients. Patients were divided into two groups (ACS and Chronic CHD). Bacteria are detected by a polymerase chain reaction assay.

Bacteria	Oral sample		Blood sample	
	ACS	Chronic CHD	ACS	Chronic CHD
Aggregatibacter actinomycetemcomitans	5 (33)*	0*	1 (7)	0
Porphyromonas gingivalis	14 (93)	10 (77)	0	0
Prevotella intermedia	10 (67)	7 (54)	0	0
Tannerella forsythia	15 (100)	12 (92)	0	0
Treponema denticola	12 (80)	11 (85)	4 (27)	2 (15)

Bacterial positive numbers (percentage). ACS: acute coronary syndrome ($n = 15$). Chronic CHD: chronic coronary heart disease ($n = 13$).
* $p < 0.05$.

relationship between periodontal pathogens and the progression of ACS.

2.2. Peripheral vascular disease

Peripheral vascular disease (PVD) is a condition where an obstruction of the blood flow in large peripheral arteries/veins, often due to the formation of a thrombus, leads to lower extremity ischemic ulceration or gangrene. The symptoms are intermittent claudication, rest pain, trophic changes in the involved limb, numbness in the extremities, and more. The most serious cases (up to 20—25% of these patients) require amputation [25].

PVD shares a common underlying pathological change with atherosclerosis, coronary heart diseases and stroke [26]. The relationship between periodontitis and atherosclerosis has been assumed since the initial observations that periodontal pathogens were identified from atheromatous plaques [14,27]. The association of periodontitis and PVD has only been reported in a few studies. Mendez et al. [28] followed up 1110 subjects over the 25 years and reported that subjects with periodontal disease at baseline had a 2.27-fold increment in the risk of developing PVD in comparison to those who had no periodontal disease at baseline (95% CI = 1.32—3.90, $p = 0.003$). This relationship was significant even after the adjustment for age, body mass index (BMI), family history of heart disease, and smoking. Hung et al. [29] also conducted a prospective cohort study ($n = 342$, 12-year follow up) and reported an increased risk of PVD in subjects with periodontal disease at baseline (RR 1.41, 95% CI = 1.12—1.77), after adjustment for age, smoking, BMI, family history of heart disease, hypertension, diabetes, hypercholesterolemia, and occupation. Lu et al. [30] conducted a cross-sectional study of 3585 subjects and performed a multiple regression analysis. Thirty-three percent or more sites of periodontal attachment loss (PAL) > 3 mm are associated with a >2-fold increase in the risk of PVD after adjusting for other risk factors. Systemic markers of inflammation {C-reactive protein (CRP), white blood cell count, fibrinogen} were also associated with PVD and PAL, suggesting that the inflammation led by oral infections may be an important pathway linking periodontitis and PVD.

A recent case-control study evaluated the association between periodontitis and peripheral arterial disease (PAD) in the Japanese population (Table 2) [31]. Twenty-five PAD patients and 32 healthy control subjects participated in the study. The results revealed that PAD patients showed higher titers against periodontopathic bacteria, such as *P. gingivalis* and *Treponema denticola*, and those organisms could be detected in atherosclerotic specimens using the polymerase chain reaction (PCR). In addition, periodontitis increased the risk of having PAD 5-fold (95% CI = 1.57—18.89, $p = 0.007$), after adjusting for age gender, diabetes and smoking. These aforementioned studies therefore support the hypothesis of an association between periodontal disease and PVD. However, further studies are necessary to determine whether periodontitis is a causal factor associated with PVD.

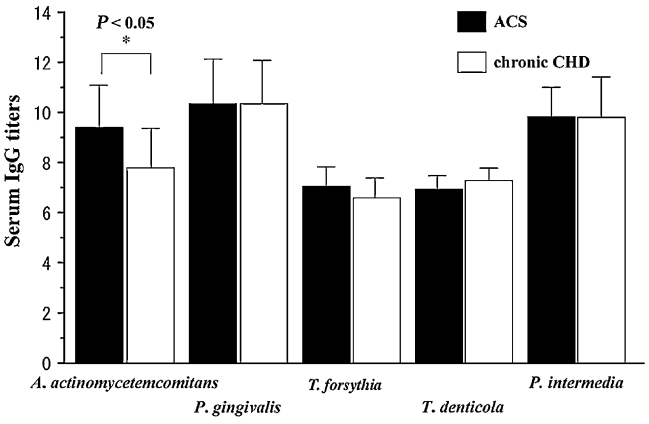

Figure 1 Serum IgG titers of periodontopathic bacteria in coronary heart disease patients. ACS; acute coronary syndrome patients, chronic CHD: chronic coronary heart disease patients.

Table 2 Association of several risk factors with peripheral arterial disease in a logistic regression model. Independent variables include periodontitis, smoking, age, gender, and diabetes.

Independent variables	Dependent variable: PAD Odds ratio (95% CI)	*p*-Value
Periodontitis	5.45 (1.57—18.89)	0.007
Smoking	0.75 (0.13—4.43)	0.754
Age	0.99 (0.94—1.05)	0.813
Gender	1.65 (0.18—15.61)	0.611
Diabetes	0.18 (0.03—1.12)	0.065

95% CI: 95% confidence interval.

Table 3 Presence of periodontopathic bacteria in an oral sample, arterial (aneurysmal) wall and mural thrombus of AAA patients. Bacteria are detected by a polymerase chain reaction assay.

Bacteria	Oral sample (n = 32)	Aneurysmal wall	Mural thrombus
All bacteria studied	28 (88)	24/28 (86)	14/16 (88)
Aggregatibacter actinomycetemcomitans	1 (3)	0/1 (0)	0
Campylobacter rectus	11 (34)	5/11 (45)	1/7 (14)
Porphyromonas gingivalis	26 (81)	22/26 (85)	12/15 (80)
Prevotella intermedia	13 (41)	4/13 (31)	0/7 (0)
Prevotella nigrescens	6 (19)	1/6 (17)	0/3 (0)
Tannerella forsythia	23 (72)	5/23 (22)	0/13 (0)
Treponema denticola	19 (59)	12/19 (63)	3/10 (30)

Oral samples: bacterial positive numbers (percentage). Arterial (aneurysmal) wall, Mural thrombus: bacterial positive ratio to positive finding of those in oral samples (percentage).

2.3. Abdominal aortic aneurism

The abdominal aorta is the largest artery in the abdominal cavity and supplies blood to much of this region. As part of the aorta, it is a direct continuation of the descending aorta. In elderly men, the infrarenal abdominal aortic diameter is between 15 and 24 mm.

An aneurism is defined as a permanent and irreversible localized dilation of a vessel. The definition of an abdominal aortic aneurism (AAA) is an aorta with an infrarenal diameter greater than 30 mm or 1.5 times the expected normal diameter [32]. There are many causes of aneurismal dilation, such as trauma, acute infection (brucellosis, salmonellosis), chronic infection (tuberculosis), inflammatory diseases (Behcet and Takayasu disease), and connective tissue disorders (Marfan Syndrome, Ehlers-Danlos type IV). However, few AAAs are the direct consequence of specific causes. Therefore, most AAAs are called non-specific. Moreover, because this disorder is invariably associated with a severe atherosclerotic damage of the aortic wall, it has been traditionally regarded as a consequence of atherosclerosis.

Histologically, AAAs are characterized by the destruction of elastin and collagen in the media and adventitia, smooth-muscle cell loss with thinning of the medial wall, infiltration of lymphocytes and macrophages, and neovascularization [33]. Production and activation of various proteases and cytokines contribute to the development of this disorder, although the underlying mechanisms are unknown.

The pathogenesis of AAA has been suggested to involve four mechanisms including the proteolytic degradation of aortic wall connective tissue, inflammation and immune responses, biomechanical wall stress, and molecular genetics [34].

Recent data suggest that chronic infection may play a role in the pathogenesis of atherosclerosis, and several infectious agents, including *C. pneumoniae*, oral bacteria, and herpes virus may be involved. *C. pneumoniae* has also been detected in the walls of AAA [35,36].

In addition, periodontopathic bacteria are present in AAA and might play a role in the development of AAA. *A. actinomycetemcomitans* is detected from both the blood and subgingival plaque samples in endarteritis and mycotic aortic aneurysm patients [37]. Another group also reported that *A. actinomycetemcomitans*, but not bacteria of the red complex [38], is detected in aortic aneurysms [39]. However, Okuda et al. showed the presence of *T. denticola* in aneurysm specimens using PCR methods and immunofluorescence microscopy [40].

Periodontopathic bacteria are present in a high percentage of specimens (86%) of diseased arteries of AAA patients, whose oral samples (saliva or subgingival bacterial plaque) are positive for periodontopathic bacteria [41]. *P. gingivalis* and *T. denticola* are frequently detected among aneurismal walls and oral samples (Table 3). These results suggest that periodontitis might be associated with AAA.

Figure 2 (a) A Buerger's disease patient. Ulceration and gangrene are observed in the fingers and toes. (b) A Buerger's disease patient. Severe recession and deep periodontal pockets are observed in this patient.

2.4. Buerger's disease

Buerger's disease (also known as thromboangiitis obliterans) is a non-atherosclerotic, segmental, inflammatory occlusive vascular disease. It mainly affects medium-sized arteries, veins, and the nerves of the extremities, and causes claudication or rest pain. In advanced cases, ulceration and gangrene are observed at the fingers and toes (Fig. 2a), often resulting the need for amputation of the involved areas.

The diagnosis of this disease is usually made based on the clinical symptoms. Its criteria generally include the following: (a) history of smoking; (b) onset before the age of 50 years; (c) infrapopliteal, segmental arterial occlusions; (d) either upper limb involvement or phlebitis migrans; and (e) absence of exclusion of atherosclerotic risk factors other than smoking [42]. The overall incidence in the world has been steadily declining but it is still more prevalent in Asian countries than in Europe or North America [43]. The pathological mechanisms of Buerger's disease are still largely unknown, although many etiologic factors have been suggested. Tobacco smoking is the only indisputable etiologic factor of Buerger's disease [42,43], although smoking alone does not seem to be sufficient to cause the disease. An autoimmune response may also implicated in the onset of Buerger's disease, and several studies have reported etiologic factors of the disease, including disorders of T-cell and B-cell mediated humoral immunity [44,45], cellular sensitivity to collagen [46,47], and HLA patterns [48]. However, these theories cannot account for the formation of phlebitis migrans, a principal characteristic of Buerger's disease, or explain why this disease affects both arteries and veins simultaneously and, occasionally, nerves. The various features of Buerger's disease might be better explained by considering the disease as a systemic reaction to bacterial infection or to an antigen originating from bacteria rather than as an immunological disorder.

Allen and Brown note the possibility that oral infection serves as a contributory factor of the inflammation of Buerger's disease [49], while no previous study has reported that specific pathogens were identified in the vessel lesion. Periodontitis as a chronic bacterial infectious disease was involved in Buerger's disease, and thus the association between periodontitis and pathogenic bacteria was investigated [50,51]. These are the first studies to report a relationship between Buerger's disease and periodontitis. Buerger's disease patients exhibited poor periodontal conditions (Fig. 2b). Periodontopathic bacteria such as *P. gingivalis* and *T. denticola* were detected in both saliva and arterial specimens of the Buerger's disease patients by a PCR analysis, while none of the control arterial samples without Buerger's disease was positive for these bacteria. Furthermore, Buerger's disease patients showed higher IgG titers against periodontopathic bacteria, thus indicating that these bacteria might trigger immune responses and play a significant role in the pathogenesis of Buerger's disease.

3. Potential mechanisms of the association between periodontitis and CVD

Some studies have suggested that potential links between periodontitis and CVD include direct effects from bacteria and indirect effects through host inflammatory responses as well as autoimmune responses. Since the DNA of *P. gingivalis* has been detected in atherosclerotic plaques [14,52] and periodontal infections can result in bacteremias and endotoxemias in the patients [53—55], systemic effects on the cardiovascular system through these exposures seem biologically reasonable. Three potential mechanisms of the association between periodontitis and CVD include:

- direct bacterial effects on platelets and host cells,
- systemically or locally induced inflammatory mediators,
- autoimmune responses.

Platelets play a critical role in hemostasis and thrombosis. *In vitro* studies on the interaction of platelets with two bacteria found in the oral cavity, *Staphylococcus aureus* and *Streptococcus sanguis*, have shown that the bacteria can induce platelet aggregation [56—58]. Recent studies have demonstrated that *P. gingivalis* can also activate platelets, induce platelet aggregation and increase protease activity [59—61]. An ultrastructural study of *P. gingivalis*-induced platelet aggregation was conducted using electron microscopy [62]. A sharp and rapid increase of small-sized platelet aggregates was observed immediately after the addition of *P. gingivalis* to human platelet rich plasma (PRP), followed by the formation of medium- and large-sized aggregates in 2—3 min. Furthermore, *P. gingivalis* was mostly present between the adherent platelets and some were internalized in platelet vacuoles by phagocytosis. Based on these findings, a similar pathologic process can be extrapolated to occur in the human cardiovascular system.

The direct effects of periodontopathic bacteria on host cells may contribute to the link between periodontitis and CVD. Invasion and/or uptake of bacteria in endothelial cells and monocytes have been reported [63]. Several groups of investigators have identified periodontal pathogens including *P. gingivalis* and *A. actinomycetemcomitans* in cardiovascular specimens [13,14,52,63]. In addition, a previous study showed that *P. gingivalis* can invade aortic and heart endothelial cells via fimbriae [64]. When human macrophages are incubated with low density lipoprotein and *P. gingivalis*, the bacteria are internalized in macrophages and significantly increase foam cell formation, the hallmark of early atherogenesis [65]. The *P. gingivalis* LPS fraction markedly upregulate ICAM-1 and VCAM-1 in human umbilical vein endothelial cells (HUVECs) and facilitate mononuclear cell adhesion to HUVECs [66]. These results suggest that a periodontal infection by *P. gingivalis* may promote monocyte recruitment to the vascular endothelium and contribute to atherogenesis.

Periodontitis and CVD potentially share similar hallmarks of inflammation. Several lines of evidence indicate that tissue destruction in periodontitis is more related to host inflammatory responses than the detrimental direct effects of the periodontopathic bacteria themselves. Atherosclerosis is currently viewed as a progressive inflammatory process rather than as simply an accumulation of lipids. Various inflammatory signals and markers including high sensitivity CRP (hsCRP), fibrinogen, and various inflammatory cytokines {i.e. interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)-alpha}, are involved in atherothrombogenesis [17,67].

Furthermore, hsCRP is the strongest biomarker for predicting cardiovascular events [68]. Inflammation, as reflected in the concentration of hsCRP, precedes the onset of cardiovascular events, confirming that atherothrombosis is, at least in part, an inflammatory disorder. It should be noted that the inflammatory mediators involved in CVD have also been reported to be associated with periodontitis. Periodontopathic bacteria can gain access to the blood circulation and have been detected in human cardiovascular specimens [63,69]. Therefore, the potential mechanism for linkage between periodontitis and CVD is inflammation, in which periodontopathic bacteria induce host cells to produce inflammatory cytokines either systematically or locally and these cytokines in turn play important roles in the development or progression of CVD.

Circulating immune cells as well as serum inflammatory mediators are activated in periodontitis patients. It has been proposed that a systemic hyper-inflammatory monocyte state might place a patient at risk for both periodontitis and atherosclerosis [21]. The findings that $CD14^{+}CD16^{+}$ monocytes and $CD45RA^{+}$ monocytes increase in chronic and aggressive periodontitis, respectively, suggest that monocytes in periodontitis patients have activated surface phenotypes in comparison to the periodontally healthy subjects. Furthermore, $CD14^{+}CD16^{+}$ monocytes produce more IL-6 than $CD16^{-}$ monocytes in response to LPS from *Escherichia coli* and *A. actinomycetmcomitans,* thus suggesting that $CD14^{+}CD16^{+}$ monocytes represent the hyper-inflammatory phenotype [70].

In addition to the effects of inflammatory responses on CVD, molecular mimicry has been suggested as a potential mechanism of the association between infection and CVD. The term ''molecular mimicry'' was coined by R. Damian in 1964, who was the first to suggest that antigenic determinants of microorganisms may resemble antigenic determinants of their host. Damian suggested that this similarity serves as a defense mechanism of a microorganism against the host's immune system and prevents the development of an immune response to the microorganism, thereby protecting it from the host defense. Years later, the term ''molecular mimicry'' was attributed a different meaning namely, antigenic determinants of microorganisms might elicit an autoimmune response that harms the host [71]. An infection with *H. pylori* induces anti-heat shock protein (HSP) antibody and HSP-specific T lymphocytes by molecular mimicry. The presence of anti-HSP60 antibodies and HSP60-specific T lymphocytes may increase the risk of atherosclerosis [72]. Autoimmune responses caused by the molecular mimicry between periodontopathic bacteria and HSP have also been reported [73,74]. Yamazaki et al. [75] showed that antibody levels to human HSP60 and *P. gingivalis* HSP60 (GroEL) are highest in patients with atherosclerosis, followed by periodontitis patients and healthy subjects. Patients with atherosclerosis have HSP60-reactive as well as GroEL-reactive T cells and that atherosclerotic lesions are infiltrated with HSP60-reactive T cells. These studies suggest the mechanism of molecular mimicry between HSP and periodontopathic bacteria to be a possible link between periodontitis and atherosclerosis.

In addition to CVD, periodontitis is also associated with an adverse pregnancy outcome [12,76]. An autoimmune disease, anti-phospholipid-antibody syndrome is associated with both CVD and adverse pregnancy outcome. The major clinical symptoms of anti-phospholipid syndrome are recurrent thrombosis, fetal loss, and premature atherosclerosis [77]. The anti-phospholipid antibody has pro-thrombotic activity, and elevated level of the antibody is a hallmark of anti-phospholipid syndrome. Among the anti-phospholipid antibodies, beta-2-glycoprotein-I-dependent anti-cardiolipin (anti-CL) antibody, and lupus anticoagulant (LA) are major groups of antibodies increased in anti-phospholipid syndrome patients. Different clinical and experimental studies of the beta-2-glycoprotein-I molecule have linked an infection to the development of anti-phospholipid syndrome [71]. Based on the remarkable similarity between the symptoms of anti-phospholipid syndrome and the reported systemic sequelae of periodontitis, as well as the likely infectious origin of anti-CL antibodies, Schenkein et al. [78] hypothesized that periodontal infection might induce production of anti-phospholipid antibodies. They reported that the prevalence of patients with chronic periodontitis and generalized aggressive periodontitis positive for anti-CL was greater than that in healthy controls.

Blank et al. identified a hexapeptide (TLRVYK) sequence in beta-2-glycoprotein-I which is recognized by a monoclonal anti beta-2-glycoprotein-I antibody, and the monoclonal antibody which is elicited in the experimental anti-phospholipid syndrome in mice. Various microbial pathogens, including *Haemophilus influenzae*, *Neisseria gonorrheae* or tetanus toxoid, bear a homologous sequence to TLRVYK peptides. Immunization of mice with these microbial pathogens induce anti-phospholipid syndrome [79].

The homologous sequence in periodontopathic bacteria was searched in the Swiss plot database, and a sequence

Table 4 Molecular mimicry between beta-2-glycoprotein I (β2GPI) and bacterial peptides. According to the Swiss plot database, homologous sequences with TLRVYK on β2GPI were found in several periodontopathic bacteria, including *A. actinomycetemcomitans*, *P. gingivalis* and *T. denticola*.

Antigens	Peptide sequence	
β2 Glycoprotein I	152—157	CA**TLRVYK**GG
Tetanus toxoid	956—958	SFW**LRV**KVSA
	1224—1226	DRI**LRV**GYNA
	1245—1249	AVK**LR**DL**K**TY
P. gingivalis gingipain	181—185	TK**TLR**I**Y**TEI
T. denticola phosphoglycerate kinase	320—329	PK**TL**AL**YK**EI
A. actinomycetemcomitans leukotoxin c	120—123	FRSI**RVYK**GS

homologous to TLRVYK was thus revealed in the to reside in leucotoxin c of *A. actinomycetemcomitans* (SIRVYK), phosphoglycerate kinase of *T. denticola* (TLALYK) and *P. gingivalis* gingipain (TLRIYT; Table 4). The effects of *A. actinomycetemcomitans* infection on the antibody response against SIRVYK peptides were examined in patients with periodontitis. The level of anti-SIRVYK antibodies was significantly higher in chronic periodontitis patients who were *A. actinomycetemcomitans*-positive than in negative patients. The anti-TLRVYK antibody levels significantly correlated with anti-SIRVYK IgG antibody levels. The results suggested that *A. actinomycetemcomitans* infection might elicit anti-SIRVYK IgG antibodies and modify the anti-TLRVYK antibody response in patients with periodontitis by molecular mimicry with beta2GPI. The molecular mimicry between periodontopathic bacteria and beta2GPI might be a relevant mechanism that enhances the risk of CVD in periodontitis patients [80].

4. Effects of periodontal treatment on cardiovascular diseases

An elevation of CRP is currently regarded as a biomarker of systemic inflammation and increased risk for CVD [81]. hsCRP has been shown to be the strongest biomarker for predicting cardiovascular events [68]. A recent meta-analysis of 10 cross-sectional studies showed that CRP in periodontitis patients is elevated in comparison to controls without periodontitis [82]. In addition, the presence of *P. gingivalis* in periodontitis patients is associated with increased CRP levels, suggesting that the elimination of the periodontopathic bacteria might reduce the serum CRP levels [83]. Available data from pilot studies suggests that periodontal intervention can improve surrogate serum biomarkers and vascular responses associated with CVD. Results from a meta-analysis indicate that the periodontal treatment could lower the levels of CRP after therapy [82]. Furthermore, a recent multi-centered randomized control study (the Periodontitis and Vascular Events; PAVE) showed that periodontal treatment can reduce the CRP levels from high to moderate levels in non-obese periodontitis patients [84]. However, race/ethnicity is known to affect CRP, and CRP levels in Asian adults are lower than in Westerners [85]. As the distribution of serum CRP level is skewed toward lower levels in the Japanese population, it is difficult to detect significant changes of serum CRP after periodontal therapy in Japanese population [86,87].

Other biomarkers significantly associated with the risk of cardiovascular events are serum amyloid A, sICAM-1, IL-6, homocysteine, total cholesterol, low density lipoprotein (LDL) cholesterol [16]. Among them, the IL-6 plasma levels in the upper quartile of the considered normal range are independently predictive of an increased risk of premature death or future myocardial infarction, even after accounting for the CRP level in large prospective studies of healthy populations [66,88]. IL-6 is also a marker for identifying patients with unstable coronary artery disease independent of other risk indicators [89]. The patients with plasma levels of IL-6 higher than 5 pg/ml have increased mortality. The plasma IL-6 levels are also different among ethnic groups. The mean levels of IL-6 in Chinese (1.1 pg/ml) are lower than those in African American (1.7 pg/ml), Hispanic (1.7 pg/ml) and non-Hispanic white (1.5 pg/ml). After adjustment for age, gender, ethnicity, smoking, diabetes, hypertension, dyslipidemia and BMI, 1-SD increments in the IL-6 levels are associated with the increased odds for peripheral arterial disease [90]. These results suggest that IL-6 might also be used as a surrogate marker to examine the effect of periodontitis on cardiovascular diseases.

Although the data from intervention studies have suggested that the values of serum markers of inflammation may significantly decrease after periodontal treatment, they

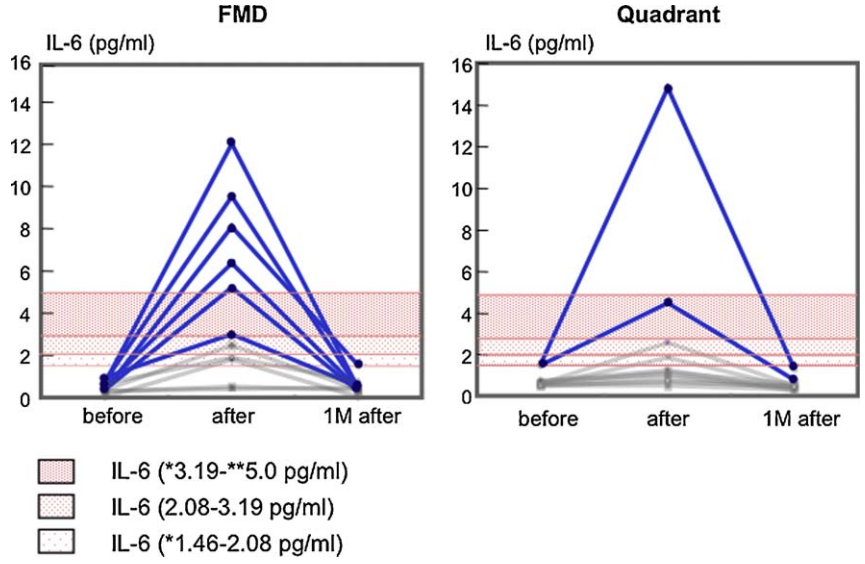

Figure 3 Fluctuations of serum IL-6 following quadrant or full-mouth mechanical debridement. Sera from chronic periodontitis patients were collected before, immediately after and 1 month after mechanical debridement, and serum IL-6 was examined by ELISA. *Higher IL-6 levels were associated with a 2-fold greater risk of death (relative risk for the highest quartile (>3.19 pg/ml) in comparison to the lowest quartile of (<1.9)) (Ref. [88]). **The unstable coronary artery disease patients with plasma levels of IL-6 higher than 5 pg/ml had increased mortality (Ref. [89]).

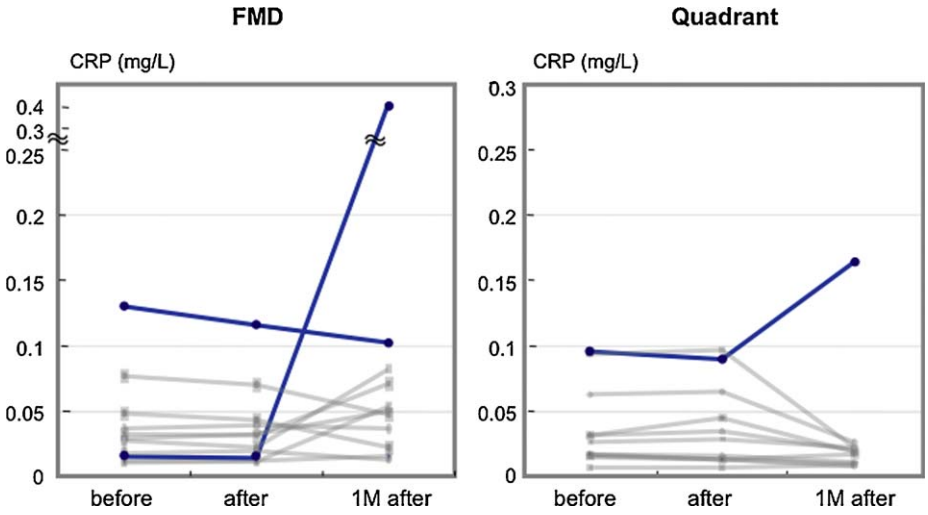

Figure 4 Fluctuations of serum CRP following quadrant or full-mouth mechanical debridement. Sera from chronic periodontitis patients were collected before, immediately after and 1 month after mechanical debridement, and serum CRP was examined using a highly sensitive CRP test.

were increased immediately after periodontal therapy [91]. Whether such increases in values suggest serious adverse events remains unknown. Full-mouth disinfection was introduced as a method to suppress periodontopathic bacteria by completing the scaling and root planning (SRP) in a short period of time (within 24 h). Full-mouth disinfection is based on the hypothesis that conventional quadrant-wise SRP might cause re-infection of the treated sites from the un-treated quadrants. There are clinical benefits of single-visit full-mouth mechanical debridement (FMD) over quadrant-wise mechanical debridement (QMD) [92]. Furthermore, the effects of the treatments on the levels of serum IL-6 and CRP were examined [87]. A transient increase of serum IL-6 is observed in both treatment groups, and it is higher in the FMD group than in the QMD group (Fig. 3). The mean CRP levels are increased in the FMD group and decreased in the QMD group at 1 month after treatment, although the difference between the two groups is not statistically significant (Fig. 4). These results suggest a potential effect of periodontal treatment on systemic inflammation.

Presently, the available evidence demonstrating the beneficial effects of periodontal intervention directly on CVD is still limited. A recent randomized controlled trial (RCT) revealed that intensive periodontal therapy results in an improvement in endothelial function after 6 months [93]. However, further properly powered longitudinal case control studies and intervention RCT are still needed. To design and carry out such studies could be problematic due to financial and ethical concerns. Both periodontitis and CVD are chronic in nature, and those chronic inflammatory conditions may develop over a number of years before the diseases are diagnosed. It is conceivable that the contributory effects of periodontitis on cardiovascular disease take place over a similarly extended period of time. Therefore, it may be difficult to reduce future cardiovascular events or symptoms by simply treating periodontal disease at the time when one or both diseases are diagnosed since the damage might have already occurred over the decades and become largely irreversible. Nevertheless, clinicians and patients should recognize the consistent association between periodontal diseases and CVD along with the potential preventive benefits of appropriate periodontal intervention. Further investigations are warranted to determine the benefits of periodontal therapy on the development and progression of CVD.

5. Conclusion

Based on the findings of studies carried out by this group and others on coronary artery diseases, peripheral arterial diseases, abdominal aortic aneurysm, and Buerger's disease, an association between periodontitis and CVD is therefore strongly suggested. The potential mechanisms of the association between periodontitis and CVD are not fully understood. However, inflammation and autoimmune mechanisms, including molecular mimicry between periodontopathic bacteria and host molecules, are suggested to be the relevant mechanisms which link periodontitis to CVD. The effects of periodontal treatment on CVD might be different among the different treatment modalities. Further studies should therefore be conducted to elucidate the effects of periodontal therapy on the prevention of CVD.

Acknowledgments

Part of this work was supported by the grants from the 21th Century Center of Excellence Program (COE) for Frontier Research on Molecular Destruction and Reconstruction of Tooth and Bone in Tokyo Medical and Dental University, and Japan Society for the Promotion of Science (JSPS) Invitation Fellowship for Research in Japan (N.W.).

References

[1] Libby P, Ridker P, Maseri A. Inflammation and atherosclerosis. Circulation 2002;105:1135—43.
[2] Libby P. Inflammation and cardiovascular disease mechanisms. Am J Clin Nutr 2006;83:456S—60S.

[3] Zambon J. Periodontal diseases: microbial factors. Ann Periodontol 1996;1:879—925.
[4] Offenbacher S. Periodontal diseases: pathogenesis. Ann Periodontol 1996;1:821—78.
[5] Khader Y, Albashaireh Z, Alomari M. Periodontal diseases and the risk of coronary heart and cerebrovascular diseases: a meta-analysis. J Periodontol 2004;75:1046—53.
[6] Meurman J, Sanz M, Janket S. Oral health, atherosclerosis, and cardiovascular disease. Crit Rev Oral Biol Med 2004;15:403—13.
[7] Vettore M. Periodontal disease and cardiovascular disease. Evid Based Dent 2004;5:69.
[8] Bahekar A, Singh S, Saha S, Molnar J, Arora R. The prevalence and incidence of coronary heart disease is significantly increased in periodontitis: a meta-analysis. Am Heart J 2007;154:830—7.
[9] Mustapha I, Debrey S, Oladubu M, Ugarte R. Markers of systemic bacterial exposure in periodontal disease and cardiovascular disease risk: a systematic review and meta-analysis. J Periodontol 2007;78:2289—302.
[10] Paquette D, Brodala N, Nichols T. Cardiovascular disease, inflammation, and periodontal infection. Periodontol 2000 2007;44:113—26.
[11] Persson G, Persson R. Cardiovascular disease and periodontitis: an update on the associations and risk. J Clin Periodontol 2008;35(8 Suppl.):362—79.
[12] Kinane D, Bouchard P. Periodontal diseases and health: Consensus Report of the Sixth European Workshop on Periodontology. J Clin Periodontol 2008;35(8 Suppl.):333—7.
[13] Chiu B. Multiple infections in carotid atherosclerotic plaques. Am Heart J 1999;138(5 Pt 2):S534—6.
[14] Haraszthy V, Zambon J, Trevisan M, Zeid M, Genco R. Identification of periodontal pathogens in atheromatous plaques. J Periodontol 2000;71:1554—60.
[15] Lalla E, Lamster I, Hofmann M, Bucciarelli L, Jerud A, Tucker S, et al. Oral infection with a periodontal pathogen accelerates early atherosclerosis in apolipoprotein E-null mice. Arterioscler Thromb Vasc Biol 2003;23:1405—11.
[16] Ridker P, Hennekens C, Buring J, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. N Engl J Med 2000;342:836—43.
[17] Ridker P, Silvertown J. Inflammation, C-reactive protein, and atherothrombosis. J Periodontol 2008;79(8 Suppl.):1544—51.
[18] Beck J, Offenbacher S. Oral health and systemic disease: periodontitis and cardiovascular disease. J Dent Educ 1998;62: 859—70.
[19] Fong I. Emerging relations between infectious diseases and coronary artery disease and atherosclerosis. CMAJ 2000;163:49—56.
[20] Paunio K, Impivaara O, Tiekso J, Mäki J. Missing teeth and ischaemic heart disease in men aged 45—64 years. Eur Heart J 1993;14(Suppl. K):54—6.
[21] Beck J, Garcia R, Heiss G, Vokonas P, Offenbacher S. Periodontal disease and cardiovascular disease. J Periodontol 1996;67(10 Suppl.):1123—37.
[22] DeStefano F, Anda R, Kahn H, Williamson D, Russell C. Dental disease and risk of coronary heart disease and mortality. BMJ 1993;306:688—91.
[23] Brodala N, Merricks E, Bellinger D, Damrongsri D, Offenbacher S, Beck J, et al. *Porphyromonas gingivalis* bacteremia induces coronary and aortic atherosclerosis in normocholesterolemic and hypercholesterolemic pigs. Arterioscler Thromb Vasc Biol 2005;25:1446—51.
[24] Sakurai K, Wang D, Suzuki J, Umeda M, Nagasawa T, Izumi Y, et al. High incidence of actinobacillus actinomycetemcomitans infection in acute coronary syndrome. Int Heart J 2007;48:663—75.
[25] Dormandy J, Rutherford R. Management of peripheral arterial disease (PAD). TASC Working Group. TransAtlantic Inter-Society Consensus (TASC). J Vasc Surg 2000;31(1 Pt 2):S1—296.
[26] Selvin E, Erlinger T. Prevalence of and risk factors for peripheral arterial disease in the United States: results from the National Health and Nutrition Examination Survey, 1999—2000. Circulation 2004;110:738—43.
[27] Okuda K, Ishihara K, Nakagawa T, Hirayama A, Inayama Y. Detection of *Treponema denticola* in atherosclerotic lesions. J Clin Microbiol 2001;39:1114—7.
[28] Mendez M, Scott T, LaMorte W, Vokonas P, Menzoian J, Garcia R. An association between periodontal disease and peripheral vascular disease. Am J Surg 1998;176:153—7.
[29] Hung H, Willett W, Merchant A, Rosner B, Ascherio A, Joshipura K. Oral health and peripheral arterial disease. Circulation 2003;107:1152—7.
[30] Lu B, Parker D, Eaton C. Relationship of periodontal attachment loss to peripheral vascular disease: an analysis of NHANES 1999—2002 data. Atherosclerosis 2008;200:199—205.
[31] Chen Y, Umeda M, Nagasawa T, Takeuchi Y, Huang Y, Inoue Y, et al. Periodontitis may increase the risk of peripheral arterial disease. Eur J Vasc Endovasc Surg 2008;35:153—8.
[32] Thompson R, Geraghty P, Lee J. Abdominal aortic aneurysms: basic mechanisms and clinical implications. Curr Probl Surg 2002;39:110—230.
[33] López-Candales A, Holmes D, Liao S, Scott M, Wickline S, Thompson R. Decreased vascular smooth muscle cell density in medial degeneration of human abdominal aortic aneurysms. Am J Pathol 1997;150:993—1007.
[34] Wassef M, Baxter B, Chisholm R, Dalman R, Fillinger M, Heinecke J, et al. Pathogenesis of abdominal aortic aneurysms: a multidisciplinary research program supported by the National Heart, Lung, and Blood Institute. J Vasc Surg 2001;34:730—8.
[35] Tanaka S, Komori K, Okadome K, Sugimachi K, Mori R. Detection of active cytomegalovirus infection in inflammatory aortic aneurysms with RNA polymerase chain reaction. J Vasc Surg 1994;20:235—43.
[36] Petersen E, Boman J, Persson K, Arnerlöv C, Wadell G, Juto P, et al. *Chlamydia pneumoniae* in human abdominal aortic aneurysms. Eur J Vasc Endovasc Surg 1998;15:138—42.
[37] Martín M, Andrés M, Fierro J, Méndez F. Endarteritis and mycotic aortic aneurysm caused by an oral strain of *Actinobacillus actinomycetemcomitans*. Eur J Clin Microbiol Infect Dis 1998;17:104—7.
[38] Holt SC, Ebersole JL. *Porphyromonas gingivalis*, *Treponema denticola*, and *Tannerella forsythia*: the "red complex", a prototype polybacterial pathogenic consortium in periodontitis. Periodontol 2000 2005;38:72—122.
[39] Marques da Silva R, Caugant D, Lingaas P, Geiran O, Tronstad L, Olsen I. Detection of *Actinobacillus actinomycetemcomitans* but not bacteria of the red complex in aortic aneurysms by multiplex polymerase chain reaction. J Periodontol 2005;76: 590—4.
[40] Okuda K, Ishihara K, Nakagawa T, Hirayama A, Inayama Y, Okuda K. Detection of *Treponema denticola* in atherosclerotic lesions. J Clin Microbiol 2001;39:1114—7.
[41] Kurihara N, Inoue Y, Iwai T, Umeda M, Huang Y, Ishikawa I. Detection and localization of periodontopathic bacteria in abdominal aortic aneurysms. Eur J Vasc Endovasc Surg 2004;28:553—8.
[42] Shionoya S. Diagnostic criteria of Buerger's disease. Int J Cardiol 1998;66(Suppl. 1):S243—5 [discussion S7].
[43] Olin J. Thromboangiitis obliterans (Buerger's disease). N Engl J Med 2000;343:864—9.
[44] Kobayashi M, Ito M, Nakagawa A, Nishikimi N, Nimura Y. Immunohistochemical analysis of arterial wall cellular infiltration in Buerger's disease (endarteritis obliterans). J Vasc Surg 1999;29:451—8.
[45] Lee T, Seo J, Sumpio B, Kim S. Immunobiologic analysis of arterial tissue in Buerger's disease. Eur J Vasc Endovasc Surg 2003;25:451—7.

[46] Adar R, Papa M, Halpern Z, Mozes M, Shoshan S, Sofer B, et al. Cellular sensitivity to collagen in thromboangiitis obliterans. N Engl J Med 1983;308:1113—6.
[47] Eichhorn J, Sima D, Lindschau C, Turowski A, Schmidt H, Schneider W, et al. Antiendothelial cell antibodies in thromboangiitis obliterans. Am J Med Sci 1998;315:17—23.
[48] Ohtawa T. HLA antigens in arterial occlusive diseases in Japan. Jpn J Surg 1976;6:1—8.
[49] Allen EV, Brown GE. Thromboangiitis obliterans. A clinical study of 200 cases. Ann Internal Med 1928;1:535—49.
[50] Chen Y, Iwai T, Umeda M, Nagasawa T, Huang Y, Takeuchi Y, et al. Elevated IgG titers to periodontal pathogens related to Buerger disease. Int J Cardiol 2007;122:79—81.
[51] Iwai T, Inoue Y, Umeda M, Huang Y, Kurihara N, Koike M, et al. Oral bacteria in the occluded arteries of patients with Buerger disease. J Vasc Surg 2005;42:107—15.
[52] Nakano K, Inaba H, Nomura R, Nemoto H, Takeuchi H, Yoshioka H, et al. Distribution of *Porphyromonas gingivalis* fimA genotypes in cardiovascular specimens from Japanese patients. Oral Microbiol Immunol 2008;23:170—2.
[53] Pussinen P, Tuomisto K, Jousilahti P, Havulinna A, Sundvall J, Salomaa V. Endotoxemia, immune response to periodontal pathogens, and systemic inflammation associate with incident cardiovascular disease events. Arterioscler Thromb Vasc Biol 2007;27:1433—9.
[54] Geerts S, Nys M, De M, Charpentier J, Albert A, Legrand V, et al. Systemic release of endotoxins induced by gentle mastication: association with periodontitis severity. J Periodontol 2002;73: 73—8.
[55] Forner L, Larsen T, Kilian M, Holmstrup P. Incidence of bacteremia after chewing, tooth brushing and scaling in individuals with periodontal inflammation. J Clin Periodontol 2006;33: 401—7.
[56] Herzberg M, Brintzenhofe K, Clawson C. Aggregation of human platelets and adhesion of *Streptococcus sanguis*. Infect Immun 1983;39:1457—69.
[57] Clawson C, Rao G, White J. Platelet interaction with bacteria. IV. Stimulation of the release reaction. Am J Pathol 1975;81: 411—20.
[58] Bayer A, Sullam P, Ramos M, Li C, Cheung A, Yeaman M. *Staphylococcus aureus* induces platelet aggregation via a fibrinogen-dependent mechanism which is independent of principal platelet glycoprotein IIb/IIIa fibrinogen-binding domains. Infect Immun 1995;63:3634—41.
[59] Curtis M, Macey M, Slaney J, Howells G. Platelet activation by Protease I of *Porphyromonas gingivalis* W83. FEMS Microbiol Lett 1993;110:167—73.
[60] Lourbakos A, Yuan Y, Jenkins A, Travis J, Andrade-Gordon P, Santulli R, et al. Activation of protease-activated receptors by gingipains from *Porphyromonas gingivalis* leads to platelet aggregation: a new trait in microbial pathogenicity. Blood 2001;97:3790—7.
[61] Sharma A, Novak E, Sojar H, Swank R, Kuramitsu H, Genco R. *Porphyromonas gingivalis* platelet aggregation activity: outer membrane vesicles are potent activators of murine platelets. Oral Microbiol Immunol 2000;15:393—6.
[62] Li X, Iwai T, Nakamura H, Inoue Y, Chen Y, Umeda M, et al. An ultrastructural study of *Porphyromonas gingivalis*-induced platelet aggregation. Thromb Res 2008;122:810—9.
[63] Schenkein H, Barbour S, Berry C, Kipps B, Tew J. Invasion of human vascular endothelial cells by *Actinobacillus actinomycetemcomitans* via the receptor for platelet-activating factor. Infect Immun 2000;68:5416—9.
[64] Deshpande R, Khan M, Genco C. Invasion of aortic and heart endothelial cells by *Porphyromonas gingivalis*. Infect Immun 1998;66:5337—43.
[65] Giacona M, Papapanou P, Lamster I, Rong L, D'Agati V, Schmidt A, et al. *Porphyromonas gingivalis* induces its uptake by human macrophages and promotes foam cell formation in vitro. FEMS Microbiol Lett 2004;241:95—101.
[66] Nakamura N, Yoshida M, Umeda M, Huang Y, Kitajima S, Inoue Y, et al. Extended exposure of lipopolysaccharide fraction from *Porphyromonas gingivalis* facilitates mononuclear cell adhesion to vascular endothelium via Toll-like receptor-2 dependent mechanism. Atherosclerosis 2008;196:59—67.
[67] Ridker P, Rifai N, Stampfer M, Hennekens C. Plasma concentration of interleukin-6 and the risk of future myocardial infarction among apparently healthy men. Circulation 2000;101:1767—72.
[68] Ridker P. Intrinsic fibrinolytic capacity and systemic inflammation: novel risk factors for arterial thrombotic disease. Haemostasis 1997;27(Suppl. 1):2—11.
[69] Spahr A, Klein E, Khuseyinova N, Boeckh C, Muche R, Kunze M, et al. Periodontal infections and coronary heart disease: role of periodontal bacteria and importance of total pathogen burden in the Coronary Event and Periodontal Disease (CORODONT) study. Arch Intern Med 2006;166:554—9.
[70] Nagasawa T, Kobayashi H, Aramaki M, Kiji M, Oda S, Izumi Y. Expression of CD14, CD16 and CD45RA on monocytes from periodontitis patients. J Periodontal Res 2004;39:72—8.
[71] Blank M, Barzilai O, Shoenfeld Y. Molecular mimicry and autoimmunity. Clin Rev Allergy Immunol 2007;32:111—8.
[72] Ayada K, Yokota K, Kobayashi K, Shoenfeld Y, Matsuura E, Oguma K. Chronic infections and atherosclerosis. Ann NY Acad Sci 2007;1108:594—602.
[73] Tabeta K, Yamazaki K, Hotokezaka H, Yoshie H, Hara K. Elevated humoral immune response to heat shock protein 60 (hsp60) family in periodontitis patients. Clin Exp Immunol 2000;120: 285—93.
[74] Tabeta K, Yoshie H, Yamazaki K. Characterization of serum antibody to *Actinobacillus actinomycetemcomitans* GroEL-like protein in periodontitis patients and healthy subjects. Oral Microbiol Immunol 2001;16:290—5.
[75] Yamazaki K, Ohsawa Y, Itoh H, Ueki K, Tabeta K, Oda T, et al. T-cell clonality to *Porphyromonas gingivalis* and human heat shock protein 60s in patients with atherosclerosis and periodontitis. Oral Microbiol Immunol 2004;19:160—7.
[76] Hasegawa K, Furuichi Y, Shimotsu A, Nakamura M, Yoshinaga M, Kamitomo M, et al. Associations between systemic status, periodontal status, serum cytokine levels, and delivery outcomes in pregnant women with a diagnosis of threatened premature labor. J Periodontol 2003;74:1764—70.
[77] Levine J, Branch D, Rauch J. The antiphospholipid syndrome. N Engl J Med 2002;346:752—63.
[78] Schenkein H, Berry C, Burmeister J, Brooks C, Barbour S, Best A, et al. Anti-cardiolipin antibodies in sera from patients with periodontitis. J Dent Res 2003;82:919—22.
[79] Blank M, Krause I, Fridkin M, Keller N, Kopolovic J, Goldberg I, et al. Bacterial induction of autoantibodies to beta2-glycoprotein-I accounts for the infectious etiology of antiphospholipid syndrome. J Clin Invest 2002;109:797—804.
[80] Wang D, Nagasawa T, Chen Y, Ushida Y, Kobayashi H, Takeuchi Y, et al. Molecular mimicry of Aggregatibacter actinomycetemcomitans with beta2 glycoprotein I. Oral Microbiol Immunol 2008;23:401—5.
[81] Ridker P, Buring J, Cook N, Rifai N. C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14 719 initially healthy American women. Circulation 2003;107:391—7.
[82] Paraskevas S, Huizinga J, Loos B. A systematic review and meta-analyses on C-reactive protein in relation to periodontitis. J Clin Periodontol 2008;35:277—90.
[83] Pitiphat W, Savetsilp W, Wara-aswapati N. C-reactive protein associated with periodontitis in a Thai population. J Clin Periodontol 2008;35:120—5.
[84] Offenbacher S, Beck JD, Moss K, Mendoza L, Paquette DW, Barrow DA, et al. Results from the periodontitis and vascular

events (PAVE) Study: a pilot multicentered, randomized, controlled trial to study effects of periodontal therapy in a secondary prevention model of cardiovascular disease. J Periodontol 2009;80:190—201.

[85] Yamada S, Gotoh T, Nakashima Y, Kayaba K, Ishikawa S, Nago N, et al. Distribution of serum C-reactive protein and its association with atherosclerotic risk factors in a Japanese population: Jichi Medical School Cohort Study. Am J Epidemiol 2001;153:1183—90.

[86] Yamazaki K, Honda T, Oda T, Ueki-Maruyama K, Nakajima T, Yoshie H, et al. Effect of periodontal treatment on the C-reactive protein and proinflammatory cytokine levels in Japanese periodontitis patients. J Periodontal Res 2005;40:53—8.

[87] Ushida Y, Koshy G, Kawashima Y, Kiji M, Umeda M, Nitta H, et al. Changes in serum interleukin-6, C-reactive protein and thrombomodulin levels under periodontal ultrasonic debridement. J Clin Periodontol 2008;35:969—75.

[88] Harris T, Ferrucci L, Tracy R, Corti M, Wacholder S, Ettinger WJ, et al. Associations of elevated interleukin-6 and C-reactive protein levels with mortality in the elderly. Am J Med 1999;106:506—12.

[89] Lindmark E, Diderholm E, Wallentin L, Siegbahn A. Relationship between interleukin 6 and mortality in patients with unstable coronary artery disease: effects of an early invasive or non-invasive strategy. JAMA 2001;286:2107—13.

[90] Allison M, Criqui M, McClelland R, Scott J, McDermott M, Liu K, et al. The effect of novel cardiovascular risk factors on the ethnic-specific odds for peripheral arterial disease in the Multi-Ethnic Study of Atherosclerosis (MESA). J Am Coll Cardiol 2006;48:1190—7.

[91] D'Aiuto F, Nibali L, Parkar M, Suvan J, Tonetti M. Short-term effects of intensive periodontal therapy on serum inflammatory markers and cholesterol. J Dent Res 2005;84:269—73.

[92] Koshy G, Kawashima Y, Kiji M, Nitta H, Umeda M, Nagasawa T, et al. Effects of single-visit full-mouth ultrasonic debridement versus quadrant-wise ultrasonic debridement. J Clin Periodontol 2005;32:734—43.

[93] Tonetti M, D'Aiuto F, Nibali L, Donald A, Storry C, Parkar M, et al. Treatment of periodontitis and endothelial function. N Engl J Med 2007;356:911—20.