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Review Article

Current evidence and biological plausibility linking periodontitis to atherosclerotic cardiovascular disease

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Summary The relationship between poor oral health and systemic diseases has been increasingly recognized over the past two decades. Atherosclerosis is an important basal component of atherosclerotic cardiovascular disease (ACVD), which is the *primary* cause of death worldwide, including Japan.

The accumulation of multiple individual epidemiological studies has paved the way for subsequent systematic reviews that have demonstrated that periodontitis can be considered as an emerging risk factor for ACVD. Although the causal mechanisms by which periodontitis accelerates ACVD have not been fully elucidated, plausible evidence regarding the inflammatory response due to inflammatory mediators and bacterial etiologies, and the recognition of altered lipid metabolism in patients with periodontitis suggest that infection with periodontopathic bacteria can influence atherogenesis *in vitro* and *in vivo*. Animal model studies have strengthened this evidence. However, there have been a lack of interventional studies that show the effects of periodontal treatment on the future risk of ACVD; this lack of evidence critically weakens the importance of the relationship between the two diseases. This review presents a summary of the current evidence and biological plausibility that link periodontitis to ACVD.

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Contents

1. Introduction

Periodontitis is caused by infection with a group of bacteria, primarily Gram negative and anaerobic species. The inflammation triggered by a bacterial infection is characterized by mononuclear cell infiltration into the gingival tissues, leading to connective tissue destruction and alveolar bone resorption. The loss of tooth function caused by periodontal destruction diminishes masticatory function and impairs facial configuration. Furthermore, periodontitis is a major public health issue because it can be a source of social inequality, decreases quality of life, and increases dental costs; it also has a potential impact on systemic diseases.

Individual epidemiological studies and subsequent systematic reviews have demonstrated that periodontitis can be considered as an emerging risk factor for atherosclerotic vascular disease (ACVD) [1]. Although the causal mechanisms by which periodontitis accelerates ACVD have not been fully elucidated, plausible evidence regarding the inflammatory response due to inflammatory mediators and bacterial etiologies, and the recognition of altered lipid metabolism in patients with periodontitis suggest that infection with periodontopathic bacteria can influence atherogenesis (Fig. 1). Several studies conducted *in vitro* and using animal models have demonstrated some causal mechanisms in human patients with periodontitis; these mechanisms suggest that infection and the subsequent inflammatory response may be a key to elucidating the association between atherosclerosis and periodontitis. This review presents a summary of recent studies on the relationship between periodontitis and ACVD.

2. Epidemiological evidence

The association between poor oral health and ACVD has been increasingly recognized over the past two decades. A significant number of groups have conducted epidemiological studies, and the findings have been systematically reviewed several times [1–6]. A comprehensive review by an American Heart Association (AHA) working group concluded that periodontal disease is associated with atherosclerotic vascular disease independent of known confounders [7,8]. However, the working group further concluded that there was no evidence of a causal link. This review further pointed out gaps in the published research and methodological issues that should be improved in future research, such as the need for uniform criteria for the evaluation and case definitions of periodontitis. It further emphasized the need for well-designed, controlled interventional studies with standard treatment protocols as well as considerations for issues such as sustainability of treatment response over time [7,8]. To this point, Dietrich et al. [9] systematically reviewed cohort and case–control studies while minimizing the effects of misclassification by including studies that evaluated periodontal probing depth/clinical attachment loss and/or radiographically assessed alveolar bone loss. The researchers observed that the association was stronger in younger adults and that there was no evidence for an association between periodontitis and the incidence of coronary heart disease (CHD) in subjects aged >65 years. The conclusions from this review were that the evidence for an increased risk of ACVD in patients with periodontitis compared with that in patients without the disease only applied to a limited section of the population [9]. Thus, the clinical parameters of periodontitis, such as periodontal probing depth, clinical attachment loss, and/or radiographic assessment of bone loss, have all been associated with an increased risk of ACVD independent of established risk factors. However, the amount of excess risk adjusted for ACVD risk factors varied across studies according to the type of cardiovascular outcome and age and sex of the subjects. Specifically, the risk has been greater in males and younger individuals [9–12].

3. Biological plausibility

3.1. Inflammatory mediators

Atherosclerosis, an inflammatory disease, is the major cause of ACVD and is initiated by injury to the vascular endothelium [13–16]. It is a major cause of diseases that involve plaque formation, plaque disruption, and subsequent atherothrombosis [14,17]. Although the accumulation of atheromatous

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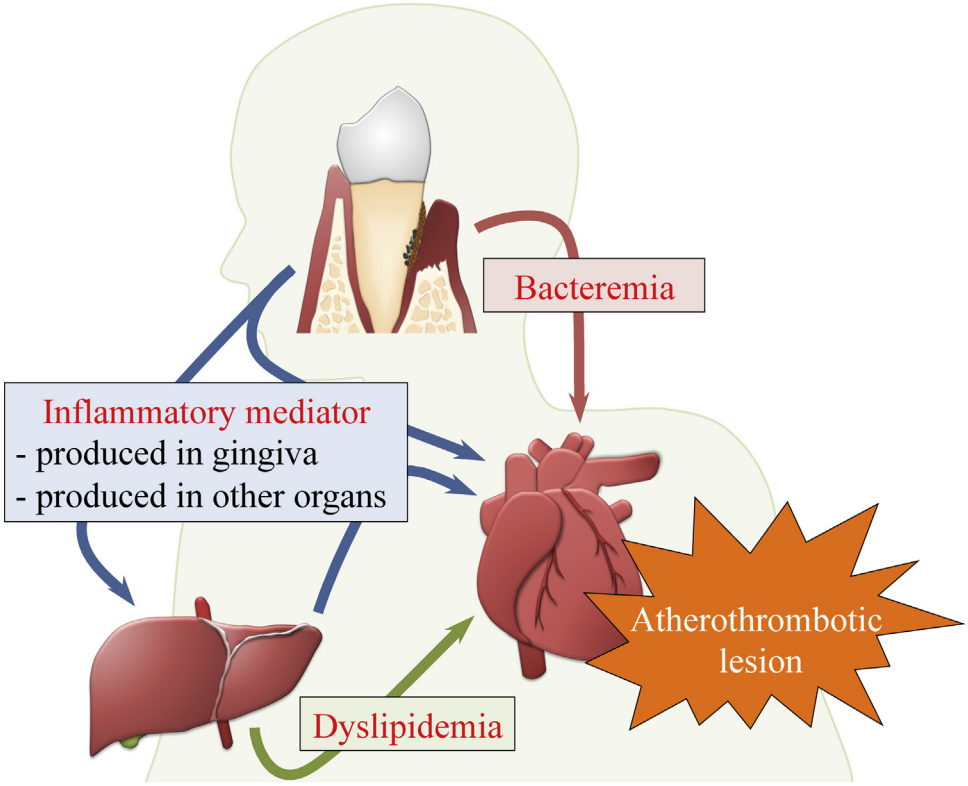

Figure 1 Biological plausibility of the relationship between the development of atherothrombotic lesions and periodontal infection. Bacteria entering the circulation as a result of periodontal infection, dental procedures, and routine tooth care result in varying levels of bacteremia. This may enhance the progression of atherosclerotic cardiovascular disease (red arrow). Inflammatory mediators produced in infected gingival tissues or as part of the hepatic response to periodontal infection may enhance the progression of atherosclerotic cardiovascular disease (blue arrow). Dyslipidemia modulated by periodontal infection primarily affecting the hepatic response may enhance the progression of atherosclerotic cardiovascular disease (green arrow). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

plaques in the artery wall is characteristic of atherosclerosis, the nature of the inflammatory response in the artery wall may be modulated by chronic infectious diseases that directly supply pathogens into the blood stream or indirectly influence systemic inflammation [18]. Endothelial dysfunction, the earliest indicator of cardiovascular disease, may be modulated through a state of systemic inflammation that can be evaluated by measuring different factors such as acute phase protein (CRP), tumor necrosis factor-a (TNF-α), and interleukin-6 (IL-6), which have also been reported to be elevated in patients with periodontitis [19—21].

High-sensitivity CRP (hsCRP) has been identified to be a key marker of atherosclerosis, and elevated levels constitute a risk factor for ACVD [22—25]. The mechanisms of CRP production in periodontitis patients have not been clearly demonstrated. CRP is produced mainly in the liver in response to IL-6, but extrahepatic production has also been confirmed at sites such as in the endothelium of atherosclerotic plaques, smooth muscle cells, infiltrated macrophages, and inflamed gingival tissues [26—28]. Serum hsCRP levels are much higher among Western individuals than among Japanese individuals. Whereas an hsCRP level of $>$2 mg/L represents a high risk of CHD development among Western populations, 1 mg/L is the critical level among the Japanese [29]. Nakajima et al. found that the number of patients with serum hsCRP levels $>$1 mg/L decreased after periodontal therapy in a Japanese population, suggesting that periodontal therapy may potentially decrease CHD risk in this population [19].

The TNF-α concentration is reportedly higher in the serum of patients with periodontitis than in the serum of healthy subjects [30]. The effects of periodontal therapy on serum TNF-α concentration in patients with periodontitis were observed in multiple groups [31—33]. On the other hand, other study groups failed to detect the effects of periodontal therapy [19,34—38]. The concept of the elevation of TNF-α in patients with periodontitis has been controversial. The fact that the degree of elevation of TNF-α may be lesser than that of CRP and IL-6 may decrease the statistical power for detecting significance in studies with small patient samples. IL-6, a proinflammatory cytokine that can trigger systemic inflammation and hepatic CRP production, asserts its functions in an autocrine manner by way of the IL-6 receptor [26,27]. Two randomized controlled trials (RCT) reported a decrease in serum IL-6 concentrations in patients with periodontitis [39,40] and this finding was in line with those of other studies [41,42]. However, no significant effect of periodontal treatment was observed in other studies [36,43]. A recent meta-analysis also failed to detect the effects of periodontal therapy on decreasing serum IL-6 levels; the authors concluded that there was moderate evidence that did not support the effects of nonsurgical therapy on serum IL-6 concentrations [44].

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3.2. Bacteremia

Periodontal bacteria enter the circulation following dental procedures such as scaling, tooth extraction, and periodontal probing. Routine tooth care or activities such as tooth brushing, flossing, chewing, and biting can also cause varying levels of bacteremia depending on the study design [45]. Slight levels of bacteremia, which may consistently induce low-grade inflammation several times a day in daily life, may potentially have an effect on atherogenicity.

Even if the bacteria do not survive long in the circulation, the bacterial products that remain in the blood stream, such as the outer membrane vesicles [46] and gingipains [47], may also cause systemic and endothelial inflammatory responses; however, the extent to which these bacterial components or the inflammatory cytokines derived from oral infection affect endothelial function cannot be evaluated in humans because of technical issues. An inflammatory response triggered in endothelial cells induces the production of inflammatory cytokines and chemokines and the expression of adhesion molecules on the cell surface; this is followed by the infiltration of leukocytes.

3.3. Bacterial invasion

Several groups have reported bacterial invasion of host cells through the invasion or adhesion of *Porphyromonas gingivalis*, *Aggregatibacter actinomycetemcomitans*, and *Fusobacterium nucleatum* to macrophages, vascular endothelial cells, and gingival epithelial cells [45]. It remains unclear whether the invasion of bacteria plays a role in human atherogenesis. However, internalized bacteria in epithelial cells can certainly induce the host immune response; furthermore, parts of the bacteria may flow into the blood stream, modulating the progression of atherosclerosis. A system of immune evasion of *P. gingivalis*, where the bacteria remains in a dominant state in the host cell, has been reported by one study group; this may cause a prolonged inflammatory response as observed in chronic inflammation. Using complement C5 convertase-like activity, *P. gingivalis* synergizes with C5a to increase cyclic adenosine monophosphate (cAMP) concentrations, resulting in the suppression of macrophage immune function and enhancement of pathogen survival *in vitro* and *in vivo* [48]. *P. gingivalis*, through lysine gingipain, can subvert the protective host proinflammatory response by direct cytokine degradation [49]. Invasion may provide access to host proteins, iron, and other nutrients by inducing host cell lysis or apoptosis. Egress of *P. gingivalis* from the endocytic recycling pathway in gingival epithelial cells helps in prolonging infection [50]. These observations may partly account for the persistence of periodontal inflammation and may influence the host inflammatory response. Downregulation or evasion of immune function may give bacteria the benefit of being able to survive, as observed in inflammatory exudates such as gingival crevicular fluid.

3.4. Periodontal bacteria in the atheromatous tissues

Several species of oral bacteria have been identified in the affected disease sites of ACVD patients. Genomic DNA, mainly 16S rRNA DNA, from periodontopathic bacteria and other species were detected by polymerase chain reaction (PCR); however, the frequency of detection of different species varies [51–59]. Controversially, no detection of bacterial DNA in atheromatous specimens has also been reported by some researchers [60–62]. Multiple groups have attempted to detect live periodontopathic bacteria in atheromatous plaques. *P. gingivalis* and *A. actinomycetemcomitans* were detected in endothelial cells derived from homogenized atheromatous tissue cultures through specific antibody detection [63]. Fresh atheromatous cells cultured with macrophages enabled the detection of *P. gingivalis* in culture [64]. However, this evidence does not necessarily indicate the actual invasion of live bacteria on site because the observation was obtained with cell cultures. Namely, the bacteria from contaminated blood may have invaded cultured cells *in vitro*; therefore, further studies are needed to confirm these findings. Nevertheless, these reports do indicate the possible immunological interaction between live bacteria and atheromatous plaque cells because the invasion of *P. gingivalis* into human cardiovascular cells such as human coronary artery endothelial cells (HCAECs), human aortic endothelial cells (HAECs), and human microvascular endothelial cells (HMECs)-1 has been reported *in vitro* [65–69].

3.5. Effect of periodontitis on lipid metabolism

Atherosclerosis is characterized by inflammatory cell infiltration, foam cell formation, and lipid accumulation in the vessel wall. Infection and inflammation are associated with marked changes in lipid and lipoprotein metabolism. Many of the changes in lipoproteins during infection/inflammation help in protecting the host from the harmful effects of the stimuli. However, in patients with chronic infection, inflammatory diseases, diabetes, obesity, and metabolic syndrome, these cytokine-induced changes in the structure and function of lipoproteins can be deleterious and may contribute to the development of atherosclerosis [70]. Therefore, it is of interest to determine whether periodontitis has an effect on lipid metabolism.

Severe periodontitis has been associated with a modest decrease in the levels of high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol concentrations and a more robust increase in plasma triglyceride concentrations [71,72]. HDL cholesterol is an anti-atherogenic lipoprotein [73,74], and a low HDL cholesterol concentration has been established as an independent risk factor for CHD [75].

In contrast, no difference in HDL cholesterol concentrations was observed in the 10,590 participants in an Israeli population study, although the total cholesterol and triglyceride concentrations were higher in the patients with periodontitis than in the controls, as determined by the community periodontal index of treatment needs [76,77]. Pussinen et al. demonstrated that high combined serum antibody levels against *A. actinomycetemcomitans* and *P. gingivalis* were significantly associated with low HDL cholesterol concentrations [78]. Furthermore, the same research group demonstrated that periodontitis decreased serum HDL cholesterol concentrations by comparing them before and after treatment [78]. Although infection and inflammation have been associated with a decrease in serum HDL cholesterol, the exact mechanism has not yet been established.

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3.6. Influence of other systemic diseases

Some risk factors such as age, gender, cigarette smoking, and presence of diabetes are common to periodontitis and ACVD. Therefore, the relationship between these two diseases has been carefully assessed considering the effect of these confounders, and periodontitis has been shown to be an independent risk factor for CHD. The influence of diseases such as diabetes is a plausible mechanism because the disease is exacerbated by periodontal infection, adversely affecting glycemic control in patients with diabetes mellitus, contributing to the development of diabetic complications [79], promoting the development of atherosclerosis, and increasing CHD risk.

Chronic kidney disease (CKD) has not received much attention in the context of the relationship between atherosclerotic disease and periodontal disease. However, the relationship between CKD and acute coronary syndromes has been well recognized [80,81]. End-stage renal disease is strongly associated with premature cardiovascular death and morbidity [82]. CKD is associated with accelerated atherogenesis, and the adverse influence of CKD has been demonstrated by the doubled mortality rate associated with acute coronary syndrome [83]. The role of chronic inflammation in the etiology of CKD was indicated by the increase in serum CRP levels [84,85]. Inflammation, oxidative stress, and dyslipidemia in advanced CKD have all been suggested to promote atherogenesis [86]. Previous studies also suggested an association between periodontitis and CKD. The atherosclerosis risk (ARIC) study demonstrated an association between CKD and periodontitis, with an OR of 2.0 (95% confidence interval, 1.23—3.24), and an exponential increase in antibodies to periodontal pathogens has been associated with CKD [87,88]. A retrospective study from the Third National Health and Nutrition Survey-NHANES III in the USA demonstrated that edentulous adults are more likely to have CKD [89]. Interventional studies in subjects with generalized chronic periodontitis demonstrated that nonsurgical periodontal therapy decreases the glomerular filtration rate (GFR), as assessed by cystatin C levels [90]. A systematic review assessing the relationship between periodontitis and CKD concluded that consistent evidence supports a positive association between the two diseases and the positive effects of periodontal treatment on GFR [91]. It is noteworthy that the only RCT study performed till date comprised a comparatively small study population; therefore, further studies are required to obtain sufficient evidence [92]. However, plausible mechanisms linking other systemic diseases such as diabetes and CKD to ACVD should be taken into account in order to understand the relationship between ACVD and periodontitis.

3.7. Animal studies

Several animal studies aimed at clarifying the effects of periodontopathic bacterial infection on atherogenesis have documented the formation of atheromatous plaque and the elevation of systemic inflammatory markers in the murine model [93—95]. Other studies observed the development of fatty streaks after periodontal infection in rabbits [96] and atherosclerotic coronary lesions in normocholesterolemic and hypercholesterolemic pigs [97]. Bacteremia and bacterial invasion have been observed in humans, and this can explain the mechanisms linking periodontal infection to atherogenesis. However, the detection of bacteria in blood or affected tissues has not been a consistent finding. Without inducing bacteremia, we demonstrated that oral infection with *P. gingivalis* enhanced atherogenesis in apolipoprotein E (ApoE)-mutant mice, notably accompanying an increase in LDL cholesterol and decrease in HDL cholesterol, with altered gene expression profiles related to cholesterol transport [98,99].

There are several points to consider before these findings can be extrapolated as a link between human periodontitis and atherosclerosis. First, intravenous inoculation with bacteria, rather than the natural route of infection for human periodontitis (*i.e.*, *via* oral tissues), was used in some experiments. Although the occurrence of transient bacteremia on manipulation of the teeth and periodontal tissues is common, the extent of bacteremia resulting from a dental procedure is relatively low [$<10^4$ colony-forming units (CFUs) of bacteria per milliliter] [100]. Moreover, there is no information on the relationship between the severity and extent of disease and the extent of bacteremia; therefore, the findings observed after the direct inoculation of bacteria may not represent those of naturally occurring periodontitis. Second, most studies used Apo E-deficient mice that phenotypically develop hyperlipidemia and atherosclerosis. Whether or not infection can be a trigger for the development of atherosclerosis in this model cannot be addressed.

4. Intervention studies

Currently, there are no interventional studies on primary (first ischemic event) ACVD prevention. There is a single interventional study in which periodontal therapy was administered as an intervention in a secondary cardiac event prevention model through five coordinated cardiology—dental centers. In this protocol, 30% of the control subjects received periodontal treatment in addition to standard care. This pilot study failed to detect any adverse effects of periodontal scaling and root planning in individuals with heart disease as compared with a community care group, which also received some treatment [101]. The management of control subjects is an issue when designing RCT intervention studies because ethical concerns can be raised in regard to the long-term withholding of periodontal treatment.

5. Conclusions

In conclusion, the current epidemiological evidence obtained from acceptable quality-controlled studies indicates the relationship between periodontitis and ACVD independent of known confounders. However, the lack of interventional studies that show the preventive effects of periodontal treatment on the future incidence of ACVD weakens the importance of the relationship between the two diseases. Interventional studies in the Japanese population are required because the original characteristics of life style, serum lipid concentrations, and genetic background need to be taken into account. These studies should be performed in multiple centers and on a large scale, and they should evaluate the feasibility of applicable treatments to contribute to public health. This review shows that we lack clinical

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markers to monitor the stability of the effects of periodontal therapy on ACVD.

Plausible evidence has been accumulated, and additional studies are required not only for better understanding and confirmation of these findings but also for the development of a novel and effective treatment or the isolation of effective markers to monitor the biological relationship between periodontitis and ACVD.

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References

[1] Humphrey LL, Fu R, Buckley DI, Freeman M, Helfand M. Periodontal disease and coronary heart disease incidence: a systematic review and meta-analysis. J Gen Intern Med 2008;23(December (12)):2079—86.
[2] Hujoel PP, Drangsholt M, Spiekerman C, DeRouen TA. Pre-existing cardiovascular disease and periodontitis: a follow-up study. J Dent Res 2002;81(March (3)):186—91.
[3] Janket SJ, Baird AE, Chuang SK, Jones JA. Meta-analysis of periodontal disease and risk of coronary heart disease and stroke. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2003;95(May (5)):559—69.
[4] Bahekar AA, 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(November (5)):830—7.
[5] Blaizot A, Vergnes JN, Nuwwareh S, Amar J, Sixou M. Periodontal diseases and cardiovascular events: meta-analysis of observational studies. Int Dent J 2009;59(August (4)):197—209.
[6] Khader YS, Albashaireh ZS, Alomari MA. Periodontal diseases and the risk of coronary heart and cerebrovascular diseases: a meta-analysis. J Periodontol 2004;75(August (8)):1046—53.
[7] Lockhart PB, Bolger AF, Papapanou PN, Osinbowale O, Trevisan M, Levison ME, et al. Periodontal disease and atherosclerotic vascular disease: does the evidence support an independent association?: a scientific statement from the American Heart Association. Circulation 2012;125(May (20)):2520—44.
[8] Tonetti MS, Van Dyke TE, working group 1 of the joint EFPAAPw. Periodontitis and atherosclerotic cardiovascular disease: consensus report of the Joint EFP/AAP Workshop on Periodontitis and Systemic Diseases. J Periodontol 2013;84(April (4 Suppl.)):S24—9.
[9] Dietrich T, Sharma P, Walter C, Weston P, Beck J. The epidemiological evidence behind the association between periodontitis and incident atherosclerotic cardiovascular disease. J Clin Periodontol 2013;40(April (14 Suppl)):S70—84.
[10] Jimenez M, Krall EA, Garcia RI, Vokonas PS, Dietrich T. Periodontitis and incidence of cerebrovascular disease in men. Ann Neurol 2009;66(October (4)):505—12.
[11] Grau AJ, Becher H, Ziegler CM, Lichy C, Buggle F, Kaiser C, et al. Periodontal disease as a risk factor for ischemic stroke. Stroke 2004;35(February (2)):496—501.
[12] Xu FY, Lu B. Prospective association of periodontal disease with cardiovascular and all-cause mortality: NHANES III follow-up study. Atherosclerosis 2011;218(October (2)):536—42.
[13] Ross R. Atherosclerosis — an inflammatory disease. N Engl J Med 1999;340(January (2)):115—26.
[14] Ruberg FL, Leopold JA, Loscalzo J. Atherothrombosis: plaque instability and thrombogenesis. Prog Cardiovasc Dis 2002;44(March—April (5)):381—94.
[15] Vita JA, Loscalzo J. Shouldering the risk factor burden: infection, atherosclerosis, and the vascular endothelium. Circulation 2002;106(July (2)):164—6.
[16] Pober JS, Min W, Bradley JR. Mechanisms of endothelial dysfunction, injury, and death. Annu Rev Pathol-Mech 2009;4:71—95.
[17] Galis ZS, Sukhova GK, Lark MW, Libby P. Increased expression of matrix metalloproteinases and matrix degrading activity in vulnerable regions of human atherosclerotic plaques. J Clin Invest 1994;94(December (6)):2493—503.
[18] Tonetti MS. Periodontitis and risk for atherosclerosis: an update on intervention trials. J Clin Periodontol 2009;36(July (10 Suppl)):15—9.
[19] Nakajima T, Honda T, Domon H, Okui T, Kajita K, Ito H, et al. Periodontitis-associated up-regulation of systemic inflammatory mediator level may increase the risk of coronary heart disease. J Periodontal Res 2010;45(February (1)):116—22.
[20] Paraskevas S, Huizinga JD, Loos BG. A systematic review and meta-analyses on C-reactive protein in relation to periodontitis. J Clin Periodontol 2008;35(April (4)):277—90.
[21] Leivadaros E, van der Velden U, Bizzarro S, Ten Heggeler JM, Gerdes VE, Hoek FJ, et al. A pilot study into measurements of markers of atherosclerosis in periodontitis. J Periodontol 2005;76(January (1)):121—8.
[22] Blake GJ, Ridker PM. High sensitivity C-reactive protein for predicting cardiovascular disease: an inflammatory hypothesis. Eur Heart J 2001;22(March (5)):349—52.
[23] Blake GJ, Ridker PM. Inflammatory bio-markers and cardiovascular risk prediction. J Intern Med 2002;252(October (4)):283—94.
[24] Blake GJ, Ridker PM. C-reactive protein: a surrogate risk marker or mediator of atherothrombosis? Am J Physiol Regul Integr Comp Physiol 2003;285(November (5)):R1250—2.
[25] Blake GJ, Rifai N, Buring JE, Ridker PM. Blood pressure, C-reactive protein, and risk of future cardiovascular events. Circulation 2003;108(December (24)):2993—9.
[26] Moshage HJ, Roelofs HM, van Pelt JF, Hazenberg BP, van Leeuwen MA, Limburg PC, et al. The effect of interleukin-1, interleukin-6 and its interrelationship on the synthesis of serum amyloid A and C-reactive protein in primary cultures of adult human hepatocytes. Biochem Biophys Res Commun 1988;155(August (1)):112—7.
[27] Maekawa T, Takahashi N, Honda T, Yonezawa D, Miyashita H, Okui T, et al. *Porphyromonas gingivalis* antigens and interleukin-6 stimulate the production of monocyte chemoattractant protein-1 via the upregulation of early growth response-1 transcription in human coronary artery endothelial cells. J Vasc Res 2009;47(4):346—54.
[28] Maekawa T, Tabeta K, Kajita-Okui K, Nakajima T, Yamazaki K. Increased expression of C-reactive protein gene in inflamed gingival tissues could be derived from endothelial cells stimulated with interleukin-6. Arch Oral Biol 2011;56(November (11)):1312—8.
[29] Arima H, Kubo M, Yonemoto K, Doi Y, Ninomiya T, Tanizaki Y, et al. High-sensitivity C-reactive protein and coronary heart disease in a general population of Japanese: the Hisayama study. Arterioscler Thromb Vasc Biol 2008;28(July (7)):1385—91.
[30] Gorska R, Nedzi-Gora M. The effects of the initial treatment phase and of adjunctive low-dose doxycycline therapy on clinical parameters and MMP-8, MMP-9, and TIMP-1 levels in the saliva and peripheral blood of patients with chronic periodontitis. Arch Immunol Ther Exp 2006;54(November—December (6)):419—26.
[31] Iwamoto Y, Nishimura F, Nakagawa M, Sugimoto H, Shikata K, Makino H, et al. The effect of antimicrobial periodontal treatment on circulating tumor necrosis factor-alpha and glycated hemoglobin level in patients with type 2 diabetes. J Periodontol 2001;72(June (6)):774—8.

Please cite this article in press as: Tabeta K, et al. Current evidence and biological plausibility linking periodontitis to atherosclerotic cardiovascular disease. Japanese Dental Science Review (2014), http://dx.doi.org/10.1016/j.jdsr.2014.03.001

[32] Iwamoto Y, Nishimura F, Soga Y, Takeuchi K, Kurihara M, Takashiba S, et al. Antimicrobial periodontal treatment decreases serum C-reactive protein, tumor necrosis factor-alpha, but not adiponectin levels in patients with chronic periodontitis. J Periodontol 2003;74(August (8)):1231—6.
[33] Duarte PM, da Rocha M, Sampaio E, Mestnik MJ, Feres M, Figueiredo LC, et al. Serum levels of cytokines in subjects with generalized chronic and aggressive periodontitis before and after non-surgical periodontal therapy: a pilot study. J Periodontol 2010;81(July (7)):1056—63.
[34] Lalla E, Kaplan S, Yang J, Roth GA, Papapanou PN, Greenberg S. Effects of periodontal therapy on serum C-reactive protein, sE-selectin, and tumor necrosis factor-alpha secretion by peripheral blood-derived macrophages in diabetes. A pilot study. J Periodontal Res 2007;42(June (3)):274—82.
[35] Kallio KA, Buhlin K, Jauhiainen M, Keva R, Tuomainen AM, Klinge B, et al. Lipopolysaccharide associates with pro-atherogenic lipoproteins in periodontitis patients. Innate Immun 2008;14(August (4)):247—53.
[36] Buhlin K, Hultin M, Norderyd O, Persson L, Pockley AG, Pussinen PJ, et al. Periodontal treatment influences risk markers for atherosclerosis in patients with severe periodontitis. Atherosclerosis 2009;206(October (2)):518—22.
[37] 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(February (1)):53—8.
[38] Sun WL, Chen LL, Zhang SZ, Wu YM, Ren YZ, Qin GM. Inflammatory cytokines, adiponectin, insulin resistance and metabolic control after periodontal intervention in patients with type 2 diabetes and chronic periodontitis. Intern Med 2011;50(15):1569—74.
[39] D'Aiuto F, Parkar M, Andreou G, Suvan J, Brett PM, Ready D, et al. Periodontitis and systemic inflammation: control of the local infection is associated with a reduction in serum inflammatory markers. J Dent Res 2004;83(February (2)):156—60.
[40] D'Aiuto F, Parkar M, Nibali L, Suvan J, Lessem J, Tonetti MS. Periodontal infections cause changes in traditional and novel cardiovascular risk factors: results from a randomized controlled clinical trial. Am Heart J 2006;151(May (5)):977—84.
[41] Higashi Y, Goto C, Jitsuiki D, Umemura T, Nishioka K, Hidaka T, et al. Periodontal infection is associated with endothelial dysfunction in healthy subjects and hypertensive patients. Hypertension 2008;51(February (2)):446—53.
[42] Fentoglu O, Koroglu BK, Kara Y, Dogan B, Yilmaz G, Sutcu R, et al. Serum lipoprotein-associated phospholipase A(2) and C-reactive protein levels in association with periodontal disease and hyperlipidemia. J Periodontol 2011;82(March (3)):350—9.
[43] Correa FO, Goncalves D, Figueredo CM, Bastos AS, Gustafsson A, Orrico SR. Effect of periodontal treatment on metabolic control, systemic inflammation and cytokines in patients with type 2 diabetes. J Clin Periodontol 2010;37(January (1)):53—8.
[44] D'Aiuto F, Orlandi M, Gunsolley JC. Evidence that periodontal treatment improves biomarkers and CVD outcomes. J Periodontol 2013;84(April (4 Suppl)):S85—105.
[45] Reyes L, Herrera D, Kozarov E, Roldan S, Progulske-Fox A. Periodontal bacterial invasion and infection: contribution to atherosclerotic pathology. J Clin Periodontol 2013;40(April (14 Suppl)):S30—50.
[46] Bartruff JB, Yukna RA, Layman DL. Outer membrane vesicles from *Porphyromonas gingivalis* affect the growth and function of cultured human gingival fibroblasts and umbilical vein endothelial cells. J Periodontol 2005;76(June (6)):972—9.
[47] Fitzpatrick RE, Wijeyewickrema LC, Pike RN. The gingipains: scissors and glue of the periodontal pathogen, *Porphyromonas gingivalis*. Future Microbiol 2009;4(May (4)):471—87.
[48] Wang M, Krauss JL, Domon H, Hosur KB, Liang S, Magotti P, et al. Microbial hijacking of complement-toll-like receptor crosstalk. Sci Signal 2010;3(109):ra11.
[49] Stathopoulou PG, Benakanakere MR, Galicia JC, Kinane DF. The host cytokine response to *Porphyromonas gingivalis* is modified by gingipains. Oral Microbiol Immunol 2009;24(February (1)):11—7.
[50] Takeuchi H, Furuta N, Morisaki I, Amano A. Exit of intracellular *Porphyromonas gingivalis* from gingival epithelial cells is mediated by endocytic recycling pathway. Cell Microbiol 2011;13(May (5)):677—91.
[51] Haraszthy VI, Zambon JJ, Trevisan M, Zeid M, Genco RJ. Identification of periodontal pathogens in atheromatous plaques. J Periodontol 2000;71(October (10)):1554—60.
[52] Stelzel M, Conrads G, Pankuweit S, Maisch B, Vogt S, Moosdorf R, et al. Detection of *Porphyromonas gingivalis* DNA in aortic tissue by PCR. J Periodontol 2002;73(August (8)):868—70.
[53] Ishihara K, Nabuchi A, Ito R, Miyachi K, Kuramitsu HK, Okuda K. Correlation between detection rates of periodontopathic bacterial DNA in coronary stenotic artery plaque [corrected] and in dental plaque samples. J Clin Microbiol 2004;42(March (3)):1313—5.
[54] 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(November (5)):553—8.
[55] Pucar A, Milasin J, Lekovic V, Vukadinovic M, Ristic M, Putnik S, et al. Correlation between atherosclerosis and periodontal putative pathogenic bacterial infections in coronary and internal mammary arteries. J Periodontol 2007;78(April (4)):677—82.
[56] Nakano K, Nemoto H, Nomura R, Inaba H, Yoshioka H, Taniguchi K, et al. Detection of oral bacteria in cardiovascular specimens. Oral Microbiol Immunol 2009;24(February (1)):64—8.
[57] Figuero E, Sanchez-Beltran M, Cuesta-Frechoso S, Tejerina JM, del Castro JA, Gutierrez JM, et al. Detection of periodontal bacteria in atheromatous plaque by nested polymerase chain reaction. J Periodontol 2011;82(October (10)):1469—77.
[58] Ohki T, Itabashi Y, Kohno T, Yoshizawa A, Nishikubo S, Watanabe S, et al. Detection of periodontal bacteria in thrombi of patients with acute myocardial infarction by polymerase chain reaction. Am Heart J 2012;163(February (2)):164—7.
[59] 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(June (3)):160—7.
[60] Cairo F, Gaeta C, Dorigo W, Oggioni MR, Pratesi C, Pini Prato GP, et al. Periodontal pathogens in atheromatous plaques. A controlled clinical and laboratory trial. J Periodontal Res 2004;39(December (6)):442—6.
[61] Aimetti M, Romano F, Nessi F. Microbiologic analysis of periodontal pockets and carotid atheromatous plaques in advanced chronic periodontitis patients. J Periodontol 2007;78(Sepetember (9)):1718—23.
[62] Aquino AR, Lima KC, Paiva MS, Rocas IN, Siqueira Jr JF. Molecular survey of atheromatous plaques for the presence of DNA from periodontal bacterial pathogens, archaea and fungi. J Periodontal Res 2011;46(June (3)):303—9.
[63] Kozarov EV, Dorn BR, Shelburne CE, Dunn Jr WA, Progulske-Fox A. Human atherosclerotic plaque contains viable invasive *Actinobacillus actinomycetemcomitans* and *Porphyromonas gingivalis*. Arterioscler Thromb Vasc Biol 2005;25(March (3)):e17—8.
[64] Rafferty B, Jonsson D, Kalachikov S, Demmer RT, Nowygrod R, Elkind MS, et al. Impact of monocytic cells on recovery of uncultivable bacteria from atherosclerotic lesions. J Intern Med 2011;270(Sepetember (3)):273—80.
[65] Deshpande RG, Khan MB, Genco CA. Invasion of aortic and heart endothelial cells by *Porphyromonas gingivalis*. Infect Immun 1998;66(November (11)):5337—43.

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[66] Dorn BR, Dunn Jr WA, Progulske-Fox A. Invasion of human coronary artery cells by periodontal pathogens. Infect Immun 1999;67(November (11)):5792–8.
[67] Rodrigues PH, Progulske-Fox A. Gene expression profile analysis of *Porphyromonas gingivalis* during invasion of human coronary artery endothelial cells. Infect Immun 2005;73(September (9)):6169–73.
[68] Takahashi Y, Davey M, Yumoto H, Gibson 3rd FC, Genco CA. Fimbria-dependent activation of pro-inflammatory molecules in *Porphyromonas gingivalis* infected human aortic endothelial cells. Cell Microbiol 2006;8(May (5)):738–57.
[69] Dolgilevich S, Rafferty B, Luchinskaya D, Kozarov E. Genomic comparison of invasive and rare non-invasive strains reveals *Porphyromonas gingivalis* genetic polymorphisms. J Oral Microbiol 2011;3:5764–74.
[70] Khovidhunkit W, Kim MS, Memon RA, Shigenaga JK, Moser AH, Feingold KR, et al. Effects of infection and inflammation on lipid and lipoprotein metabolism: mechanisms and consequences to the host. J Lipid Res 2004;45(July (7)):1169–96.
[71] Yamazaki K, Honda T, Domon H, Okui T, Kajita K, Amanuma R, et al. Relationship of periodontal infection to serum antibody levels to periodontopathic bacteria and inflammatory markers in periodontitis patients with coronary heart disease. Clin Exp Immunol 2007;149(Sepetember (3)):445–52.
[72] Shimazaki Y, Saito T, Yonemoto K, Kiyohara Y, Iida M, Yamashita Y. Relationship of metabolic syndrome to periodontal disease in Japanese women: the Hisayama Study. J Dent Res 2007;86(March (3)):271–5.
[73] Levine DM, Parker TS, Donnelly TM, Walsh A, Rubin AL. In vivo protection against endotoxin by plasma high density lipoprotein. Proc Natl Acad Sci USA 1993;90(December (24)):12040–4.
[74] Mackness MI, Durrington PN, Mackness B. How high-density lipoprotein protects against the effects of lipid peroxidation. Curr Opin Lipidol 2000;11(August (4)):383–8.
[75] Gordon DJ, Rifkind BM. High-density lipoprotein — the clinical implications of recent studies. N Engl J Med 1989;321(November (19)):1311–6.
[76] Losche W, Karapetow F, Pohl A, Pohl C, Kocher T. Plasma lipid and blood glucose levels in patients with destructive periodontal disease. J Clin Periodontol 2000;27(August (8)):537–41.
[77] Katz J, Flugelman MY, Goldberg A, Heft M. Association between periodontal pockets and elevated cholesterol and low density lipoprotein cholesterol levels. J Periodontol 2002;73(May (5)):494–500.
[78] Pussinen PJ, Jousilahti P, Alfthan G, Palosuo T, Asikainen S, Salomaa V. Antibodies to periodontal pathogens are associated with coronary heart disease. Arterioscler Thromb Vasc Biol 2003;23(July (7)):1250–4.
[79] Lalla E, Papapanou PN. Diabetes mellitus and periodontitis: a tale of two common interrelated diseases. Nat Rev Endocrinol 2011;7(December (12)):738–48.
[80] Moody WE, Chue CD, Inston NG, Edwards NC, Steeds RP, Ferro CJ, et al. Understanding the effects of chronic kidney disease on cardiovascular risk: are there lessons to be learnt from healthy kidney donors? J Hum Hypertens 2012;26(March (3)):141–8.
[81] Moody WE, Edwards NC, Madhani M, Chue CD, Steeds RP, Ferro CJ, et al. Endothelial dysfunction and cardiovascular disease in early-stage chronic kidney disease: cause or association? Atherosclerosis 2012;223(July (1)):86–94.
[82] Moody WE, Edwards NC, Chue CD, Ferro CJ, Townend JN. Arterial disease in chronic kidney disease. Heart 2013;99(March (6)):365–72.
[83] Masoudi FA, Plomondon ME, Magid DJ, Sales A, Rumsfeld JS. Renal insufficiency and mortality from acute coronary syndromes. Am Heart J 2004;147(April (4)):623–9.
[84] Stenvinkel P. New insights on inflammation in chronic kidney disease-genetic and non-genetic factors. Nephrol Ther 2006;2(July (3)):111–9.
[85] Meuwese CL, Carrero JJ, Stenvinkel P. Recent insights in inflammation-associated wasting in patients with chronic kidney disease. Contrib Nephrol 2011;171:120–6.
[86] Vaziri ND, Navab M, Fogelman AM. HDL metabolism and activity in chronic kidney disease. Nat Rev Nephrol 2010;6(May (5)):287–96.
[87] Kshirsagar AV, Moss KL, Elter JR, Beck JD, Offenbacher S, Falk RJ. Periodontal disease is associated with renal insufficiency in the atherosclerosis risk in communities (ARIC) study. Am J Kidney Dis 2005;45(April (4)):650–7.
[88] Kshirsagar AV, Offenbacher S, Moss KL, Barros SP, Beck JD. Antibodies to periodontal organisms are associated with decreased kidney function — the dental atherosclerosis risk in communities study. Blood Purif 2007;25(1):125–32.
[89] Fisher MA, Taylor GW, Papapanou PN, Rahman M, Debanne SM. Clinical and serologic markers of periodontal infection and chronic kidney disease. J Periodontol 2008;79(Sepetember (9)):1670–8.
[90] Graziani F, Cei S, La Ferla F, Vano M, Gabriele M, Tonetti M. Effects of non-surgical periodontal therapy on the glomerular filtration rate of the kidney: an exploratory trial. J Clin Periodontol 2010;37(July (7)):638–43.
[91] Chambrone L, Pannuti CM, Tu YK, Chambrone LA. Evidence-based periodontal plastic surgery. II. An individual data meta-analysis for evaluating factors in achieving complete root coverage. J Periodontol 2012;83(April (4)):477–90.
[92] Borgnakke WS. Periodontitis may be associated with chronic kidney disease, but current evidence is insufficient. J Evid Based Dent Pract 2013;13(Sepetember (3)):88–90.
[93] Gibson 3rd FC, Hong C, Chou HH, Yumoto H, Chen J, Lien E, et al. Innate immune recognition of invasive bacteria accelerates atherosclerosis in apolipoprotein E-deficient mice. Circulation 2004;109(June (22)):2801–6.
[94] Lalla E, Lamster IB, Hofmann MA, Bucciarelli L, Jerud AP, Tucker S, et al. Oral infection with a periodontal pathogen accelerates early atherosclerosis in apolipoprotein E-null mice. Arterioscler Thromb Vasc Biol 2003;23(August (8)):1405–11.
[95] Li L, Messas E, Batista Jr EL, Levine RA, Amar S. *Porphyromonas gingivalis* infection accelerates the progression of atherosclerosis in a heterozygous apolipoprotein E-deficient murine model. Circulation 2002;105(February (7)):861–7.
[96] Jain A, Batista Jr EL, Serhan C, Stahl GL, Van Dyke TE. Role for periodontitis in the progression of lipid deposition in an animal model. Infect Immun 2003;71(October (10)):6012–8.
[97] Brodala N, Merricks EP, Bellinger DA, 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(July (7)):1446–51.
[98] Maekawa T, Takahashi N, Tabeta K, Aoki Y, Miyashita H, Miyauchi S, et al. Chronic oral infection with *Porphyromonas gingivalis* accelerates atheroma formation by shifting the lipid profile. PLoS ONE 2011;6(5):e20240.
[99] Miyauchi S, Maekawa T, Aoki Y, Miyazawa H, Tabeta K, Nakajima T, et al. Oral infection with *Porphyromonas gingivalis* and systemic cytokine profile in C57BL/6.KOR-ApoE shl mice. J Periodontal Res 2012;47(June (3)):402–8.
[100] Wilson W, Taubert KA, Gewitz M, Lockhart PB, Baddour LM, Levison M, et al. Prevention of infective endocarditis: guidelines from the American heart association. J Am Dent Assoc 2007;138(June (6)):739–60.
[101] Beck JD, Couper DJ, Falkner KL, Graham SP, Grossi SG, Gunsolley JC, et al. The Periodontitis and Vascular Events (PAVE) pilot study: adverse events. J Periodontol 2008;79(January (1)):90–6.

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