Mini review

Biological foundation for periodontitis as a potential risk factor for atherosclerosis


Objectives: Links between periodontal diseases and systemic diseases have been well documented by epidemiological studies. Recently, research has shifted to elucidating the biologic mechanism for a causal relationship. One focus of interest is atherosclerosis, the underlying event of cardiovascular diseases due to its serious health impact. However, it is still not clear whether periodontopathic pathogens are truly etiologic agents or ubiquitous bystanders. This article reviews the current understanding about the molecular biological interactions between periodontal disease and atherosclerosis and the biological plausibility of periodontitis as a potential risk factor for cardiovascular disease.

Materials and methods: The current literature regarding periodontal diseases and atherosclerosis and coronary vascular disease was searched using the Medline and PubMed databases.

Results: In vitro experiments and animal models are appropriate tools to investigate the biological interactions between periodontal disease and atherosclerosis at the cell molecular level. The concepts linking both pathologies refer to inflammatory response, immune responses, and hemostasis. In particular, Porphyromonas gingivalis appears to have unique, versatile pathogenic properties. Whether or not these findings from isolated cells or animal models are applicable in humans with genetic and environmental variations is yet to be determined. Likewise, the benefit from periodontal therapy on the development of atherosclerosis is unclear. Approaches targeting inflammatory and immune responses of periodontitis and atherosclerosis simultaneously are very intriguing.

Conclusion: An emerging concept suggests that a pathogenic burden from different sources might overcome an individual threshold culminating in clinical sequela. P. gingivalis contributes directly and indirectly to atherosclerosis.

Originating in the 1960s with the landmark Framingham Heart Study, a list of classical risk factors (hyperlipidemia, hypertension, smoking, diabetes mellitus, physical inactivity, obesity, endocrine dysfunction, and abnormalities of hemostasis and thrombosis) for atherosclerosis have been identified (Table 1) (1–3). However, they were not sufficient to account for the etiology of this multifactorial pathological process. Therefore, several novel risk factors have been identified, including microbial pathogens, non-specific markers for low-grade inflammation (4), fibrinogen, C-reactive protein (CRP), leukocyte count and antibodies to heat-shock proteins (5–14).

Possible focal origin for systemic spread are the gastrointestinal system,
Table 1. Risk factors implicated in atherogenesis and periodontal disease

<table>
<thead>
<tr>
<th></th>
<th>Not modifiable</th>
<th>Modifiable</th>
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</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td>Lack of exercise</td>
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<tr>
<td>Age</td>
<td>Stress</td>
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<td>Race</td>
<td>Alcohol consumption</td>
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<tr>
<td>Family history</td>
<td>Diet</td>
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<tr>
<td>Hypertension</td>
<td>Smoking</td>
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<tr>
<td>Diabetes mellitus</td>
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<td>Infections</td>
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<tr>
<td>Body mass index</td>
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<td>C-reactive protein</td>
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<td>Homocysteine</td>
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<td>Lipoprotein a</td>
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<tr>
<td>White blood cells</td>
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<tr>
<td>Fibrinogen</td>
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<tr>
<td>Total cholesterol</td>
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<tr>
<td>Low density lipoprotein</td>
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Bold type, mutual risk factor of atherosclerosis and periodontitis; regular type, atherosclerosis risk factor.

bronchi, pharynx and periodontium that harbor various putative etiologic pathogens, namely *Helicobacter* species, *Chlamydia* species, cytomegalovirus and *Porphyromonas gingivalis* (15, 16). All putative pathogens for atherosclerosis are associated with chronic infections. *Helicobacter pylori*, *Chlamydia pneumoniae*, cytomagalovirus, and *P. gingivalis* continually sense and adapt to their environment by expressing factors associated with virulence (17). Although the contribution to atherogenesis of all putative pathogens appears to be biologically plausible, inconsistencies in statistical association [e.g. *H. pylori* (18–21)], detection in atheromatous plaques of autopsy material [*H. pylori* (22), cytomagalovirus (23)] query the validity of infection as a risk factor. The prevalence of 50% of the adults in the US with atherosclerosis and seropositivity for *H. pylori*, *C. pneumoniae*, and cytomagalovirus might represent their role as coincidental bystanders.

In this context, it is legitimate to raise the question, whether and which role *P. gingivalis* possibly could play. Extensive epidemiological studies since 1989 have analyzed data related to a statistical association of periodontal disease (24). Variations in study designs, sample number, end points for cardiovascular disease and periodontal disease, assessment of periodontium, accumulation of systemic factors and adjustment for confounding factors might explain the conflicting range of outcome. Even among prospective cohort studies the degree of association fluctuates from strong, e.g. odds ratio 2.68 (25) to negligible or no association, e.g. hazard ratio 0.79 (26). Gathering nine cohort studies in a meta-analysis, the overall relative risk settled at 1.19 (27). Interestingly, the regression analysis uncovered an overestimation of 12.9% of the results caused by residual confounding after adjustment for risk factors. This illustrates the complexity of multifactorial events.

Systemic effects of *P. gingivalis*

In order to consider periodontal disease as a risk factor for atherosclerosis, the presence of pathogens associated with periodontal disease should be localized in serum or atheromatous plaques. In addition, these pathogens should induce the release of proinflammatory cytokines. Lastly, animal models demonstrating atherosclerosis induced by periodontal pathogen should be available. Among periodontal pathogens, *P. gingivalis* has been recognized as a key pathogen and risk factor for periodontal disease (28–30). Its degree of pathogenicity has been attributed to various virulence factors. Most significant is its ability to invade epithelial cells (31, 32), connective tissue (33) and endothelial cells (34). The invasion of *P. gingivalis* is mediated through up-regulation of adhesion molecules, such as intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), P- and E-selectins, only in the presence of fimbriae. The activation of adhesion molecules is also required to bind leukocytes to endothelium, which initiates transmigration and atherogenesis (35) (Fig. 1). A systemic host response is elicited shown as elevated serum and saliva antibody to *P. gingivalis* in *P. gingivalis* infected periodontitis patients (36, 37).

*P. gingivalis* lipopolysaccharides trigger inflammatory pathways through cytokine production (tumor necrosis factor, interleukin-1, prosta-

glandin E2). The concept of ‘focus of infection’ (38) and ‘oral sepsis’ (39) holds that transient bacteremias occur from dental infection, surgical dental procedures (40, 41), periodontal probing (42), and mastication (43).

Possible etiologic roles of periodontal infections in atherogenesis include bacteria and their byproducts damaging the vessel wall and subsequent metastatic infection. These events indirectly promote atheroma formation through the inflammatory response induced by periodontal or metastatic infection (23).

Biopsy studies on carotid endarterectomy specimens have demonstrated the presence of periodontal pathogens in atheromas (44). Forty-four per cent of the atheromas were found to be positive for at least one periodontal pathogen *P. gingivalis* was identified in 26% of the samples by polymerase chain reaction.

Access of pathogens to systemic circulation has been linked to atherosclerosis and thrombus formation (45). Endothelial cell damage has been shown to be promoted by the ability of *P. gingivalis* to adhere, invade, and proliferate in coronary endothelial cells (34, 46, 47). This phenomenon is believed to interfere with the physiologic dilatory function of the vessels through the pathogen’s damage of the endothelial and smooth muscle cells (48). When the former *in vitro* findings were translated to a cohort study, this association was further strengthened, as it was found that periodontitis patients had significantly compromised flow-mediated dilatation (49).

Similar evidence has been provided in animal models, specifically the use of apolipoprotein E-deficient mice (apoE) (50). Although mice are in general resistant to atherosclerosis, inactivation of the apoE gene leads to alterations in the lipid metabolism (51). Therefore, apoE (−/−) mice are known to develop atherosclerosis spontaneously, whereas heterozygous apoE (+/−) mice are more prone to atherosclerosis compared to apoE (+/+) mice (52, 53). In conjunction with *P. gingivalis*, more pronounced effects on alveolar bone loss, foam
Cell formation and atherosclerotic lesions were consistently found in inoculated apoE null mice. *P. gingivalis* was administered by intravenous injection (54) or by oral inoculation (55). Several lines of evidence confirm a role of *P. gingivalis* on atherogenesis.

**P. gingivalis’ contribution to initiating events of atherosclerosis**

Atherosclerosis is believed to be mediated by inflammatory events (56). Atheromas are a result of the progressive accumulation of cholesterol and its esters in macrophages of the intima, termed foam cells (56–58). Cytokines have been identified in the atherosclerotic plaque to regulate recruitment of monocytes, endothelial adhesion molecules, oxidized low-density lipoproteins (LDL) uptake, smooth muscle cell proliferation, and hemostatic factors (45, 59, 60). The release of cytokine from macrophages and other cells is thought to be triggered by bacterial components leading to systemic activation of phagocytic cells, a mechanism well known to be associated with *P. gingivalis* lipopolysaccharide (57, 61). Prostaglandin E2, interleukin-1β, and tumor necrosis factor-α derived from periodontitis reach high and potent systemic levels (62). This increased release of proinflammatory cytokines actively recruits more inflammatory cells, which furthermore may result in higher counts of foam cells. For example, endothelial cells stimulated by bacterial products release monocyte attractant protein-1 (MCP-1). MCP-1 mediates transendothelial migration of monocytes via chemotaxis. Mice with deficient levels of MCP-1 have been shown to have less atherosclerotic plaque development (63). However, it has been shown that *P. gingivalis* induces MCP-1 in endothelial cells in vitro (64). This implies that *P. gingivalis* may contribute to the development of atherosclerosis. However, the molecular mechanism of this finding requires in depth elucidation.

**Development of atherosclerotic lesion requires foam cell formation**

Cholesterol-laden macrophages, or as foam cells, are indispensable in the progression of atherogenesis and plaque instability. Components of *P. gingivalis* increase the uptake of LDL in murine macrophages (65). This has also been shown to induce foam cell formation in human umbilical vein endothelial cells (66). Cholesterol accumulations in macrophages are the hallmark of atherosclerotic lesions (Fig. 1). The uptake of LDL by macrophages requires oxidation to oxLDL. The oxidation is driven by the generation of reactive oxygen intermediates in macrophages in the vessel wall in response to bacteria. Macrophages transform to foam cells and stimulate the production of proinflammatory cytokines, leading to endothelial dysfunction.

Periodontitis is known as a potent source for reactive oxygen intermediates (67). A strong correlation between

<table>
<thead>
<tr>
<th>Direct effect of <em>P. gingivalis</em></th>
<th>Cells</th>
<th>Indirect effect through periodontal inflammatory and bacterial factors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lumen</strong></td>
<td>Monocyte</td>
<td>Hsp60, Hsp90</td>
</tr>
<tr>
<td><strong>Endothelial cells</strong></td>
<td>Invasion</td>
<td>VCAM, P-selectin, E-selectin</td>
</tr>
<tr>
<td><strong>Intima</strong></td>
<td>Adhesion</td>
<td>MCP-1, oxLDL, TNF-α, IL-1β</td>
</tr>
<tr>
<td><strong>Media</strong></td>
<td>Migration</td>
<td>M-CSF, CRP</td>
</tr>
<tr>
<td></td>
<td>Differentiation</td>
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<tr>
<td></td>
<td>FOAM CELL</td>
<td>Transformation, oxLDL uptake, ROI</td>
</tr>
<tr>
<td></td>
<td>Smooth muscle cell</td>
<td>Recruitment</td>
</tr>
</tbody>
</table>

*Fig. 1. Process of atherogenesis and role of direct and indirect periodontal factors. Periodontal pathogens may directly and indirectly affect blood cells and blood vessels resulting in foam cell formation, the hallmark of atherosclerosis. CRP, C-reactive protein; Hsp, heat shock protein; IL-1β, interleukin-1β; MCP-1, monocyte attractant protein-1; M-CSF, macrophage colony-stimulating factor; oxLDL, oxidized low-density lipoprotein; PGE2, prostaglandin E2; ROI, rate of infection; TNF-α, tumor necrosis factor-α; VCAM, vascular cell adhesion molecule.*
periodontitis and lipid deposition in the aorta was shown in a rabbit model (68). Periodontitis was induced by topical application of *P. gingivalis* and the correlation remained strong, although two out of five rabbits of the *P. gingivalis*-treated group failed to develop periodontitis and lipid depo-
sitions. Future studies are needed to confirm this interesting finding.

**Immunologic response and lesion progression**

Smooth muscle cells proliferate during progression to a fibrous cap into the subendothelial space where they take up oxLDL and form extracellular matrix (58). The T-cell response further contributes to foam cell formation and smooth muscle formation through cytokine production.

Another immunologic-related mechanism involves the homology of bacterial heat shock proteins (Hsp) with host proteins, which may lead to cross-reactivity. T-cells and antibodies may recognize epitopes shared by both host and infectious organism Hsps, thereby initiating and/or perpetuating atherosclerotic plaque formation (13, 14).

Among several other human tissues, Hsp is produced in the endothelium lining the vessel wall. It responds to certain stressors, such as high blood pressure and exposure to lipopolysaccharide, by producing Hsp60 (69), antibodies and facilitating cross-reactions. This immunological cross-reaction might result in cell damage and proliferation of smooth muscle cells (70). *P. gingivalis* has an Hsp60 (71) and an Hsp90 homologue (5), which were found to cross-react with the corresponding human Hsp. It has been illustrated that patients with higher levels of anti-Hsp antibodies had less destruction of periodontal tissues (72). Conversely, the inability to produce anti-Hsp antibodies might contribute to tissue destruction induced by pathogens.

Recent animal models using immunization with human Hsp60 have confirmed the role of Hsps for atherogenesis (73, 74). Besides the significant development of fatty streaks, periodontal inflammation was present in the test group (74). A T-cell response specific to Hsp60 of *P. gingivalis* was found in the serum and atheromas of patients with periodontal disease and atherosclerosis (75–77). Interestingly, this T-cell response appears to be characteristic for *P. gingivalis*; it failed to demonstrate association with other periodontal pathogens, e.g. *Actinobacillus actinomycetemcomitans*, *Capnocytophaga sputigena*, and *Eikenella corroden* (76). Evidence suggests that *P. gingivalis* Hsps circulate in the blood and eventually cross-react with endothelium and atheroma. Immune-based therapy might be a promising approach for atherosclerosis and periodontal diseases, in particular refractory cases. Nevertheless, the molecular interactions need to be further elucidated first.

Elevated serum levels of CRP, an acute-phase reactant to inflammation, is induced by non-specific, local and systemic tissue damage, infection and inflammation. Evidence from well-conducted prospective studies identified CRP as a strong marker of future vascular events (78–81). Only high-sensitivity CRP assays are valid to predict future cardiovascular events, with a serum concentration of < 1, 1–3 and > 3 µg/ml considered as low, intermediate and high risk, respectively, for a cardiovascular event. CRP is linked to atherogenesis through production of cytokines such as interleukin-1, interleukin-6, tumor necrosis factor-α, and interferon-γ. Binding of LDL and formation of foam cells is mediated by CRP (82–85). The terminal complement complex (C5b-9) is activated (86–88). In addition to systemic effects, CRP might be amplified by local CRP accumulation in atheromas (89). Cross-sectional data revealed a positive correlation of CRP levels and markers of endothelial dysfunction (90, 91). However, the carotid intimal medial thickness detected by ultrasound failed to demonstrate a direct effect (84, 92). In contrast to studies before 2000, evidence from a large scale meta-analysis including 22 prospective studies showed a decrease in odds ratio of CRP as a marker for coronary heart disease and resulted in an overall odds ratio of 1.58 (93).

As periodontitis has a high incidence in an adult population and because of the chronic nature of the disease, it seems likely that it also affects the body systemically. The systemic effect of periodontitis has been shown in a positive association between increased CRP levels and periodontitis by several groups in cross-sectional and prospective studies (94–102). CRP appears to be consistently elevated in a dose–response fashion to the pathogenic burden of periodontal bacteria (96, 98, 103, 104). As part of the Erie County study (28), serum samples and carotid endarterectomy samples were taken from 16 subjects. These subjects had periodontal disease, defined as a mean attachment loss of ≥4 mm, and a positive history of cardiovascular disease. In a follow-up study, the serum was analyzed for CRP by enzyme-linked immunosorbent assay and immunohistochemistry (100). In the presence of both diseases, CRP was significantly elevated in 75% of the subjects, with a mean CRP level of 8.58 µg/ml, compared to 39% in the absence of both diseases and a CRP level of 1.68 µg/ml. Non-surgical intervention consisting of scaling and root planing and antibiotics resulted in reduced CRP levels (105). Interestingly, baseline CRP was elevated only in a fraction of the patients who preferentially demonstrated the decrease of CRP. This suggests that the association of CRP and periodontal disease is more dimensional. In addition, the sensitivity of the CRP testing method and its specificity for periodontitis vs. other infections have to be taken into consideration.

**Plaque stability and thrombosis**

During the progression of a fibrous plaque, atheroma cells may undergo apoptosis, necrosis, and mineralization culminating in release of lipids and further narrowing of the vessel lumen. Plaque rupture subsequently leads to thrombosis of the vessel, the underlying biological event of ischemia and myocardial infarction (56, 106, 107). The coagulation cascade is simultaneously initiated.
Destabilization of pre-existing atherosclerotic plaques occurs in the presence of vascular stenosis. Oral bacteria stimulate platelet aggregation and thrombus-like formation in vitro (108). When Streptococcus sanguis was infused in rabbits, it was shown that myocardin, infarction-like symptoms were developed in a dose-dependent manner (109). Among several periodontal pathogens, P. gingivalis was the only one to trigger platelet aggregation (110). It was demonstrated that P. gingivalis vesicles and fimbriae are critical for aggregation and adherence, respectively. Furthermore, P. gingivalis-induced platelet aggregation might precede thromboembolic events.

Matrix metalloproteinases derived from macrophages are thought to weaken the fibrous cap of the atheroma, thus promoting plaque rupture. Periodontal pathogens are known to induce matrix metalloproteinases and might contribute to plaque rupture (111). In vitro, P. gingivalis has demonstrated the ability to degrade human atheroma samples.

Clinical signs of atherosclerosis in the presence of periodontal disease

Imaging and laboratory diagnostics are suitable tools to detect subclinical evidence for atheromatous plaques and occurrence/progression. The state-of-the-art imaging diagnostics of new atheromatous plaques and occurrence/progression of vessel stenosis include high-resolution duplex scanning (ultrasound) with a 10-MHz imaging probe and 5-MHz Doppler probe. The high resolution allows valid evaluation of the intima-media thickness and changes of the carotid vessel wall over time (112, 113).

In accordance with chronic, systemic infections, a dose-dependent effect was found in severe periodontal disease related to the intima-media wall thickness of the carotid artery (114). This large-scale cross-sectional study was part of the Atherosclerosis Risk in Communities (ARIC) study. The disease definitions included an increase in vessel wall thickness by ultrasound of \( \geq 1 \text{ mm} \), and attachment loss \( \geq 3 \text{ mm in } \geq 30\% \) of sites was considered severe periodontal disease. The adjusted odds ratio was 1.3. The odds ratio was 1.6 for positive B-mode ultrasound findings of carotid artery plaque, using tooth loss as an indicator of past periodontal disease (115). The results offered first evidence for a contribution of periodontal pathogens during early atherogenesis, which strengthens the connection between periodontitis and vascular events towards a causal one.

Discussion

The focus of the relationship between cardiovascular disease and periodontal disease is shifting from a purely epidemiological association towards biologic understanding of the underlying mechanism. Current evidence provided by cross-sectional and longitudinal studies has been inconclusive. Conspicuously, several important risk factors are known to contribute to both conditions mutually (Table 1). Although adjustment for known risk factors is routinely considered in epidemiological studies, residual confounding might has to be anticipated (27).

To address the issue of causality, studies based upon plausible biologic concepts between atherogenesis and periodontal diseases are needed, using in vitro cell cultures, animal models, and controlled intervention studies based on molecular markers. Within the limitations of in vitro study models in the basic sciences, the biologic plausibility for a causal relationship seems to be coherent. Direct and indirect biologic connections between periodontitis and atherosclerosis have been demonstrated at different stages of atherogenesis (Table 2). Positive findings of periodontal pathogens in circulation and cardiovascular atherosmas are a necessary requirement for local invasion of endothelial cells and for inoculation of pre-existing atherosclerotic plaques. It is possible that P. gingivalis affects the vessel wall directly and/or indirectly via inflammatory response, immune responses, and hemostasis. The inflammatory host response does not have to be exclusively triggered by P. gingivalis. A current hypothesis suggests an additive or synergistic effect resulting from coincidental bystanders of different origins. Together as total pathogenic burden they might overcome a certain threshold resulting in unequivocal clinical significance.

The connection between various chronic infection and markers of early atherogenesis was prospectively investigated over 5 years in a large population (116). The adjusted odds ratio of 2.78 expressed the chances for participants with a chronic infection to develop atherosclerosis. A total of 36.8% of individuals suffered from chronic infections, and periodontitis was present in 2.3% of patients. It was concluded that approximately 40% of the newly developed atheromas were attributable to chronic infection. Further, bacterial endotoxins and the autoantibody Hsp60 were elevated. Bacterial load was found to correlate with the extent of atherosclerosis and even cardiovascular death, which was even stronger in patients with a high CRP level, possibly representing more inflammation (117–119). The lack of association between endodontically treated teeth and periapical pathology, generally involving only a few teeth, and cardiovascular disease cross-sectional study might support this concept (120).

Infections may potentiate the action of traditional risk factors. Nevertheless, there is no direct evidence that these organisms cause atherosclerotic lesions according to Koch’s postulates. Animal models have been used to study the pathogenesis of multifactorial diseases in an attempt to exclude potentially confounding risk factors except the one of interest. Related to P. gingivalis the accumulation of risk factors, such as genetic predisposition, diet and infection, appeared to have an additive effect on the lesions (54).

Assuming a true causal link between atherosclerosis and periodontal disease, periodontal treatment is to be expected to reduce the risk of atherosclerosis and cardiovascular disease. All other results have to be interpreted as biases attributed to confounding (121). Intervention approaches aiming
Table 2. Periodontal infection linked to atherogenesis

<table>
<thead>
<tr>
<th>Atheroma event</th>
<th>Link to <em>Porphyromonas gingivalis</em></th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct effect</td>
<td>Invasion of endothelial cells</td>
<td>(34)</td>
</tr>
<tr>
<td>Initiation of atherosclerosis</td>
<td>Activation of phagocytic cells</td>
<td>(57, 61)</td>
</tr>
<tr>
<td>Initiation of atherosclerosis</td>
<td>Elevated serum lipid levels impair</td>
<td>(123)</td>
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<tr>
<td>Initiation of atherosclerosis</td>
<td>Function of PMNs</td>
<td></td>
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<tr>
<td>Initiation of atherosclerosis</td>
<td>Induction of MCP-1</td>
<td>(65, 66)</td>
</tr>
<tr>
<td>Cytokine induction</td>
<td>PGE$_2$, IL-1$\beta$, TNF-$\alpha$ derived from periodontitis reach potent systemic levels</td>
<td>(62)</td>
</tr>
<tr>
<td>Increased CRP</td>
<td>Positive serum samples and carotid endarterectomy samples</td>
<td>(28, 100)</td>
</tr>
<tr>
<td>Lipid accumulation (fatty streak)</td>
<td>Lipid deposition in the aorta using a rabbit model following <em>P. gingivalis</em> administration</td>
<td>(68)</td>
</tr>
<tr>
<td>Immune response</td>
<td>Cross-reaction in the host tissue through antibodies produced against bacterial Hsp</td>
<td>(75–77)</td>
</tr>
<tr>
<td>Hsp homologues</td>
<td>Induction of platelet aggregation</td>
<td>(109, 110)</td>
</tr>
<tr>
<td>MMP production</td>
<td>Weakening of atherosclerotic plaque</td>
<td>(111)</td>
</tr>
</tbody>
</table>

CRP, C-reactive protein; Hsp, heat shock protein; IL-1$\beta$, interleukin-1$\beta$; MCP-1, monocyte attractant protein-1; PGE$_2$, prostaglandin 2; PMN, polymorphonuclear leukocyte; TNF-$\alpha$, tumor necrosis factor-$\alpha$.

at the elimination of periodontal pathogens using conventional periodontal therapy include antibiotics or extraction. However, intervention studies on the establishment of a decreased risk in atherosclerosis as a result of periodontal treatment have yet to be published. So far, on an epidemiological basis, edentulous patients have not been shown to have a lower risk for coronary heart disease (122). Whether or not these effects on isolated cells or in animal models are applicable in human subjects with genetic and environmental variations is yet to be determined. Compared to other infectious diseases, the treatment of chronic periodontitis on a long-term basis may prove to be more demanding due to its multifactorial etiology.

Acknowledgements

This study was supported by the University of Michigan, Periodontal Graduate Student Research Fund.

The authors do not have any financial interests, either directly or indirectly, in the products listed in the study.

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