Association between Bacterial Infection and Peripheral Vascular Disease: A Review

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Abstract

There are an increasing number of data showing a clinically important association between bacterial infection and peripheral artery disease (PAD). Bacteria suspected of being involved in PAD pathogenesis are: periodontal bacteria, gut microbiota, *Helicobacter pylori*, and *Chlamydia pneumoniae*. Infectious agents may be involved in the pathogenesis of atherosclerosis via activation of a systemic or local host immunological response to contamination of extravascular tissues or the vascular wall, respectively. A systemic immunological reaction may damage vascular walls in the course of auto-immunological cross-reactions between anti-pathogen antibodies and host vascular antigens (immunological mimicry), pathogen burden mechanisms (nonspecific activation of inflammatory processes in the vascular wall), and neuroendocrine-immune cross-talk. Besides activating the inflammatory pathway, bacterial infection may trigger PAD progression or exacerbation by enhancement of platelet reactivity, by a stimulatory effect on von Willebrand factor binding, factor VIII, fibrinogen, P-selectin activation, disturbances in plasma lipids, increase in oxidative stress, and resistance to insulin. Local inflammatory host reaction and induction of atherosclerotic plaque progression and/or instability result mainly from atherosclerotic plaque colonization by microorganisms. Despite these premises, the role of bacterial infection in PAD pathogenesis should still be recognized as controversial, and randomized, controlled trials are required to evaluate the outcome of periodontal or gut bacteria modification (through diet, prebiotics, and probiotics) or eradication (using antibiotics) in hard and surrogate cardiovascular endpoints.

Keywords

► atherosclerosis
► peripheral artery
  disease
► bacteria
► infection
► *Helicobacter pylori*
► periodontitis

Vascular diseases are still the cause of more than half of the deaths in developed countries. The role of inflammatory processes in the pathogenesis of atherosclerosis is well documented. It plays a crucial role in the initiation and promotion of atherosclerotic lesions and may lead to acute coronary syndrome by the induction of plaque instability.[1,2] In addition, inflammation is involved in the phenomenon of restenosis, the renarrowing of vessels following initially successful balloon angioplasty or stenting.[3,4] One of the most common factors affecting inflammatory process activity is infection. Although we have some data concerning the role of infection, both viral (*Cytomegalovirus* [CMV], hepatitis C virus [HCV], human immunodeficiency virus [HIV], herpes simplex virus [HSV] types 1 and 2, Epstein-Barr virus [EBV], influenza virus [IV], and varicella zoster virus [VZV]) and bacterial (*Helicobacter pylori* [Hp], *Chlamydia pneumoniae*, *Haemophilus*

influenzae, *Mycoplasma pneumoniae*, *Mycobacterium*, and periodontal pathogens), in the pathogenesis of coronary artery disease (CAD),[5–10] they still need confirmation. In spite of differences in the physiological properties of coronary and peripheral arteries,[11] the recent data suggest that bacterial, viral, fungal, or protozoal infections may affect inflammatory processes in the vascular wall and atherosclerotic plaque progression in peripheral arteries through direct contamination of the vascular wall, the acceleration of systemic immunological reactions, or a combination of both mechanisms.[7] The importance of infection in atherosclerotic processes seems to be especially persuasive in young patients in whom the presence of classic atherosclerosis risk factors, such as dyslipidemia, hypertension and diabetes mellitus, does not sufficiently explain cardiovascular disease (CVD) advancement.[8,12] Bacterial contagion may change the physiology of each of the three vascular wall layers (the intima, media, and adventitia), each of which may take part in atherosclerotic processes. The proatherogenic effect of infection on intima function results mainly from the induction of endothelial dysfunction. This pathology may lead to dysregulation in vasomotor function, thrombotic complications, and the initiation and progression of atherosclerosis.[13]

The media layer of the vascular wall, built mainly from vascular smooth muscle cells (VSMCs) and connective tissue, participates in the regulation of blood pressure and the redistribution of blood flow.[13,14] It also plays a role in atherosclerosis through the regulation of the vascular lumen, the modulation of shear stress, and as a source of VSMCs, which, via growth (proliferation and/or hypertrophy) and migration to the intima take part in the development of proliferative vascular disease, such as atherosclerosis, restenosis, graft vasculopathy, and hypertension.[13,14] Infection (e.g., *C. pneumoniae*) may affect these processes.[9,15] Other factors that may modify media layer function are: sympathetic autonomic nervous system signaling, aging (induces VSMC phenotypic modulation that could have an influence on cell senescence, loss of plasticity, and reprogramming), as well as locally (paracrine) released substances, such as platelet-derived growth factor-BB (PDGF-BB) and transforming growth factor-b (TGF-b), which are the key mediators of VSMC phenotypic switching and factors supporting their overload by lipids.[14]

The adventitia, which is the external vessel layer, is composed of adventitial compacta (built mainly from fibroblasts) and adventitial fat, identified recently as perivascular adipose tissue (PVAT). PVAT has recently been recognized as the largest endocrine organ.[13] It produces adipokines (visfatin, adiponectin, resistin, leptin, and adrenomedullin), hormones (corticosteroids and sex hormones), cytokines (TNF-α, interleukin [IL]-6, and IL-8), growth factors (visfatin, TGF-b, and PDGF-BB), and other substances (reactive oxygen species [ROS], nitric oxide [NO], hydrogen sulfide [H_2S], free fatty acids, and plasminogen activator inhibitor type 1 [PAI-1]). These substances regulate inflammation, vasoreactivity, and vascular VSMC growth, proliferation, and migration in the adjacent layers (intima and VSMC) of the vasculature.[13,16,17] The outcome of these processes could, however, be adipocyte

abnormality and inflammatory cell infiltration, leading to an imbalance in PVAT-secreted growth factors and inhibitors, tending toward VSMC growth (proliferation and/or hypertrophy) and migration, endothelial and VSMC dysfunctions, finally resulting in the development of proliferative vascular disease.[8,9,13,17] Bacterial infection, locally or via pathogen burden mechanisms, may modulate the PVAT function. Other noninfective factors affecting atherosclerotic processes through changes in PVAT function are obesity, aging, and vascular injury (e.g., during ballooning or stenting).

This article aims to review the available data regarding the role of bacterial infection in the pathogenesis of arterial and venous diseases.

The Epidemiology of Infection in the Pathogenesis of Atherosclerosis

The best-documented arguments linking infection burden with chronic atherosclerosis and their acute complications mainly concern CAD, and were recently reviewed by Sessa et al[7] and Budzyński et al.[5] Many infectious agents were suspected of being involved in atherosclerosis pathogenesis. They may show proatherogenic activity both as a single causative factor and pathogen-burden infectious agents with increase in cardiovascular event risk with an increase in the number of pathogens infecting one individual. Unfortunately, the majority of these studies were based on a comparison of the cardiovascular risk in seropositive and seronegative patients. However, because the presence of antibodies against a particular microorganism does not confirm an active infection, it seems clear that these analyses were biased. Potential bias in studies designed in this way might also result from the importance of bacterial infection which may induce an atherosclerotic process later in that person's life, and is then only maintained by additional, even noninfective, factors. This may be impossible to prove, however, due to the disappearance of the microorganism and antibodies involved initially.

We have an increasing amount of data concerning the association of periodontal bacteria, such as *Porphyromonas gingivalis*, *Tannerella forsythia*, *Prevotella intermedia*, *Aggregatibacter actinomycetemcomitans*, *Treponema denticola*, *Prevotella nigrescens*, *Fusobacterium nucleatum*, *Eikenella corrodens*, *Parvimonas micra*, and *Campylobacter rectus*, and CVD and the role of periodontal agents as a risk factor in exacerbating CVD, based on review articles, observational and case–control studies, as well as randomized control trials.[18–20] It is known that individuals with unhealthy gums have a 19% greater risk of CVD (coronary, cerebrovascular, and peripheral) than individuals without periodontitis.[21–24] Furthermore, severe periodontitis is associated with systemic inflammatory reaction and endothelial dysfunction in the general population.[25] It has also been reported that periodontal pathogens accelerate the progression of abdominal aortic aneurysm (AAA).[26] The review and meta-analysis by Orlandi et al[27] demonstrated an association between periodontitis and increased carotid intima–media thickness (c-IMT), and markers of endothelial dysfunction, such as impaired brachial artery flow-mediated dilatation (FMD).

These authors also confirmed a beneficial effect of periodontal treatment on FMD (on an average by 6.64%), indicating an improvement in endothelial function. Desvarieux et al,[28] in their prospective *Oral Infections and Vascular Disease Epidemiology Study* with 420 participants, found a significant decrease in the rate of c-IMT progression together with an improvement in clinical or microbial periodontal status after an average follow-up period of 3 years. Jung et al[29] showed that the number of missing teeth was associated with c-IMT, and bleeding on probing was associated with c-IMT only in females. Similarly, Uyar et al[30] observed a significant association between dental status, oral hygiene, carotid and popliteal artery intima–media thickness, and high-sensitivity C-reactive protein (hs-CRP) level. Increased DMFT (the number of decayed [D], missing [M], and filled [F] teeth [T]) and SLI (the Silness–Loe plaque index for evaluating oral hygiene and dental plaque) scores correlated with c-IMT. In their community-based cross-sectional study performed with 1,053 patients ≥ 40 years with 10 teeth in a multiple logistic regression analysis, Hayashida et al[31] revealed that each 1 mm increase in mean periodontal pocket depth and periodontal attachment loss was associated with an increased risk of a maximal c-IMT > 1 mm and elevated cardio-ankle vascular index. Chen et al[10] detected periodontal bacteria in 13 of the 25 (52%) atherosclerotic specimens obtained from patients with aortoiliac and/or femoropopliteal occlusive disease. After adjusting for age, gender, diabetes, and smoking, periodontitis increased fivefold the risk of having peripheral artery disease (PAD) and was associated with increased serum IL-6 and TNF-α concentrations. Independent of known confounders, such as hypertension, smoking, diabetes, low socioeconomic status, and obesity,[32] the effect of periodontitis on CVDs course was also stated in a consensus report by the Joint European Federation of Periodontology and the American Academy of Periodontology Workshop on Periodontitis and Systemic Diseases.[33] Some data also showed associations between the course of PAD and other infectious agents, including *Hp*. Mete et al[34] found higher right, left, and mean c-IMT and lower serum paraoxonase-1 (PON-1) activity in *Hp*-positive than in *Hp*-negative patients. These same observations were made while comparing *Hp* cytotoxin-associated gene A (CagA)-positive patients with CagA-negative patients in the *Hp*-negative control group. CagA seropositivity was the only factor independently associated with Doppler ultrasonography signs of carotid plaque irregularity (adjusted odds ratio [OR] 8.42, 95% confidence interval [CI] 1.58–44.64).[35] Mayr et al,[36] reporting the outcomes of the Bruneck Study, showed that increases in c-IMT in a follow-up 5 years later were significantly greater in CagA-seropositive patients but not in those infected with CagA-negative *Hp* strains, and that these relationships present a dose–response relation between anti-CagA antibodies and both c-IMT and C-reactive protein (CRP) serum concentration. In a study by Diomedi et al,[37] infection with CagA-positive *Hp* strains in patients with atherosclerotic stroke was associated with greater c-IMT and poorer short-term outcomes compared with CagA-negative patients. On the other hand, Markus et al[38] only found/observed statistically significant relationships between *Hp*-seropositivity and several

conventional cardiovascular risk factors, but did not find a significant association between *Hp* seropositivity and c-IMT after controlling for age and gender. Among *Hp*-seropositive patients, the CagA strain was associated with increased c-IMT after controlling for age and gender, but not after adjustment for other cardiovascular risk factors. In addition, in a recent meta-analysis, Chen et al[9] did not find any significant association between *C. pneumoniae* infection and carotid artery narrowing either.

The Pathomechanisms of Associations between Systemic Infection and Peripheral Artery Disease

The indirect mechanism of the influence of bacterial infection on the initiation or progression of atherosclerosis depends on the host reaction to microorganisms colonizing extravascular tissues, for example, the oral cavity, skin, or digestive tract mucosa.[5,7] The intensity of these reactions is related to (a) bacterium genotype (determining, e.g., production of cytotoxins by *Hp*, such as CagA and vacuolating cytotoxin A [VacA]); (b) host health status (e.g., other infections or comorbidities); (c) host gene polymorphism (e.g., CYP2C19 polymorphism responsible for the heterogeneity of drug metabolism [e.g., antibiotics] and intensity of inflammatory response, e.g., in fibrinogen synthesis, autoimmune reactions, and antioxidative defense); and (d) host exposure to environmental factors (e.g., aspirin, smoking, or other harmful influences).[39] At least two specific mechanisms of these interactions have been proposed. The first is a specific mimicry interaction in which antibodies against a microorganism react with the host's antigens localized in the intima, evoking an autoimmune inflammatory humoral response.[5,7] This type of mechanism was confirmed by an immunohistochemical cross-reaction between the CagA antigen expressed by some *Hp* strains and the protein presented by unstable atherosclerotic plaques, such as endothelium-derived heat shock proteins (HSPs), tropomyosin, and Ca^{2+}-transporting ATPases.[6,7,40,41] Rožanković et al[42] reported that CagA antibody titers were significantly higher in symptomatic patients with carotid artery narrowing than those who were asymptomatic. Moreover, in the first group, positive immunoreactivity between monoclonal anti-CagA antibodies and the antigens of atherosclerotic specimens obtained during carotid endarterectomy was significantly higher than among asymptomatic patients, suggesting the role of an autoimmune mimicry interaction in the destabilization of carotid atherosclerotic plaques. The consequences of such reactions may be endothelial dysfunction and atherosclerosis promotion or progression.[7] The second pathway connecting infection with the presence of vasculitis or atherosclerosis progression is the so-called pathogen burden mechanism, which involves nonspecific host inflammatory pathway stimulation and the oversynthesis of proatherogenic mediators (e.g., CRP, IL-18, IL-1 β, IL-6, and tumor necrosis factor-α) and an increase in adhesion molecule expression (e.g., vascular cell adhesion molecule 1 [VCAM-1] and intercellular adhesion molecule 1 [ICAM-1]).[7,8,43–47] The source of the

above-mentioned cytokines may be either the systemic immunological system or PVAT.[16,17,48] Such a pathomechanism is proposed as an explanation of the proatherogenic action of *Hp* infection[8] and periodontal bacterial and viral infections (CMV, HCV, HIV, HSV, IV, and VZV).[7,18–20,49] According to this pathomechanism, the risk of a cardiovascular event is related to the number of infectious agents. In the work by Zhu et al,[50] the prevalence of CAD was 48, 69, and 85% in individuals with seropositivity to ≤ two pathogens, to three or four pathogens, and to five pathogens, respectively. In a study by Espinola-Klein et al,[51] the number of infectious pathogens (among them *C. pneumoniae*, *Hp*, *H. influenzae*, *M. pneumoniae*, CMV, EBV, and HSV), divided into 0 to 3, 4 to 5, and 6 to 8 seropositivities, was significantly associated with the progression of atherosclerosis (an increase of c-IMT ≥ 0.1 mm/year or progression of carotid stenosis within a follow-up period of 2.5 years), with odds ratios of 1.8 (95% CI 1.1–2.9) for 4 to 5 and 3.8 (95% CI, 1.6–8.8) for 6 to 8 compared with 0 to 3 seropositivities after adjustment for age, sex, cardiovascular risk factors, hs-CRP plasma concentration, and statin intake. The relationship between infectious burden and maximum carotid plaque thickness was also found in the northern Manhattan study.[52] In a study by Corrado et al,[53] cerebrovascular or cardiovascular events occurred in 18% of the patients during a 5-year follow-up period. The events were predicted in a multivariate analysis by the presence of high levels of fibrinogen and CRP, increased c-IMT or asymptomatic carotid plaque, seropositivity to CagA-positive *Hp* strains and to *C. pneumoniae*, and the total burden of infections.

The above-mentioned mediators of the inflammatory process could influence atherosclerosis progression, instability, and cardiovascular event occurrence, both by immunological action upon the vascular wall (the induction of endothelial and microvascular dysfunction, as well as humoral and cellular response in PVAT), and by sympathetic autonomic nervous activation, via neuroendocrine-immune cross-talk mediated by TNF-α, IL-1, and IL-6, which stimulates the hypothalamus, brain stem, and pituitary-suprarenal axis.[43,44,54–61] The potential consequences of induced autonomic nervous system imbalance and metabolic disturbance may include: (a) induction of hypertension, insulin resistance, or diabetes, (b) the production of metabolic abnormalities, such as decreased high-density lipoprotein (HDL) cholesterol and increased serum levels of low-density lipoprotein (LDL) cholesterol and triglyceride,[62] (c) ROS overproduction and LDL-lipoprotein oxidation[63,64]; in a study by Başyiğit et al,[65] c-IMT, total oxidant status, total antioxidant capacity, oxidative stress index, and serum triglyceride concentration were increased in *Hp*-positive patients compared with those who were *Hp*-negative; and (d) hyperfibrinogenemia, altered blood coagulation, leukocytosis, and platelet activation and aggregation.[43,44,54,55,66,67]

The influence of bacterial infection on the above-mentioned metabolic disorders has been confirmed in interventional studies which found, for example, favorable changes in plasma lipids after *Hp* eradication or periodontitis treatment.[18–20,68–71] On the other hand, Elizalde et al[72] did not find such a *Hp*-eradication effect, and a meta-analysis by

Deng et al[73] showed that periodontal treatment has no significant influence on the serum concentration of CRP, total cholesterol, LDL cholesterol, and triglycerides, although it improves HDL-cholesterol level. On the one hand, the disorders mentioned may explain the intermediate infection effect on the occurrence of vascular lesion progression or instability and, on the other, may act as confounding factors masking the effect of infection and requiring proper adjustment in any statistical analysis evaluating independent cardiovascular risk related to infection. Opponents of the clinical importance of bacterial infection in vascular disease induction or progression suggest that the reported association between vascular disease and infection results not only from their interplay but also from the effect of common risk factors predisposing to both of these clinical conditions (both to infection and disease). It is also underlined that the coexistence of infection with some diseases acts in a bidirectional way to aggravate their harmful activity or decrease the efficacy of treatment with antibiotics.[32,74,75] This may have resulted in biasing outcomes of cohort studies. As the most common factors associated both with some infections and the occurrence of vascular events, the following were reported as a source of bias: diabetes mellitus,[75–81] smoking,[76,77,82] and low socioeconomic level.[82–86] On the contrary, many authors confirm the independent effect of periodontal or *Hp* gastric colonization on cardiovascular endpoint occurrence in well-designed investigations, in which no imbalance in the prevalence of respective comorbidities between *Hp*-positive and *Hp*-negative patients could be found.[49,54,55,69–71,76,77,87–90] In a study by Chen et al,[8] in patients with increased c-IMT, serum IL-18 and *Hp* immunoglobulin G (IgG) were independently correlated and were significantly higher than in subjects with normal c-IMT. The study also suggested a positive association between *Hp* infection and subclinical carotid artery atherosclerosis mediated by IL-18.

The above-mentioned association between acute and chronic periodontitis and CVD[19,20] may also be explained by host immune response to pathogen antigens, although it was demonstrated that periodontal bacteria may colonize atherosclerotic plaques in the course of bacteremia (oral-hematogenic spread) and act locally.[7] In the work by Kosaka et al,[91] the Community Periodontal Index (CPI) correlated with all salivary inflammatory cytokines and the adjusted odds ratios for carotid atherosclerosis of c-IMT in the highest quartile of IL-6 and TNF-α were higher than those in the lowest quartiles. These data were interpreted by the authors as suggesting that salivary inflammatory cytokines were associated with both periodontal disease and carotid atherosclerosis. Tapashetti et al[19] found that patients with chronic periodontitis had a higher CRP plasma level and a greater mean c-IMT value than patients with healthy gums. Moreover, in a study by Caúla et al,[20] designed as a randomized clinical trial, a significant reduction of erythrocyte sedimentation rate (ESR) and triglycerides was found after 2 months of nonsurgical periodontal treatment, as well as a significant decrease in median values of CRP, ESR, total cholesterol, and triglycerides was found after 6 months. However, de Boer et al,[92] investigating the associations of circulating antibodies against periodontal pathogen

levels with 1-year cardiovascular outcomes, as well as the extent of coronary atherosclerosis, plaque vulnerability, and lesion remodeling on intravascular ultrasound (IVUS) imaging, did not find any evidence of a substantial role of systemic exposure to periodontal pathogens in CAD patients.

Currently, we also have more information on the relationships between intestinal microflora disturbances and cardiovascular complications via systemic host immune responses to bacterial antigens.[57,93–98] Gut microbiota is universally recognized as an active organ that can modulate the overall host metabolism by promoting multiple functions, from digestion to the systemic maintenance of overall host physiology, from development of the intestinal immune system to hepatic and energy metabolism, and to modulation of the brain in terms of behavior development and motor activity.[93,99] Patients who had experienced an atherosclerotic event have been found to have higher levels of *Collinsella* and lower levels of *Eubacterium* and *Roseburia* in their gut microbiota than healthy control patients.[96] Moreover, specific forms of gut microbiota were found in the blood of patients with diabetes and atherosclerotic plaque. Such observations were the basis of a hypothesis regarding the putative role of gut microbiota dysbiosis-induced atherosclerosis.[93] Gut microbiota may potentially exert a direct proatherogenic influence via atherosclerosis plaque colonization through the bloodstream after events that disturb the gut barrier (*Chryseomonas*, *Veillonella*, and *Streptococcus* have been found in atherosclerotic plaques),[96] and an intermediate effect via (a) neuro-immune cross-talk,[43,44,54–61] (b) taking part in the regulation of reverse cholesterol transport,[100–102] (c) as a source of endotoxins accelerating pathogen burden mechanisms in the host,[7] and (d) via associations with several diseases, including diabetes and obesity, which are recognized as cardiovascular risk factors.[96] It has also been suggested that the hepatic production of trimethylamine-N-oxide (TMAO) from gut microbiota-derived trimethylamine (TMA) may enhance cardiovascular risk via promoting atherosclerotic lesion development. TMA production via gut microbiota appears to originate from two principal sources: phosphatidylcholine/choline and/or L-carnitine.[96,99,103,104]

Recognizing the interrelationships between gut microbiota and peripheral artery atherosclerosis is of potential interest because of the anatomical association between the gut, the aorta, and the iliac arteries (especially in obese patients with a thick layer of metabolically and immunologically active PVAT), as well as the potential for prophylactic and therapeutic antiatherogenic interventions using diet modification (fermentable fibers and plant polyphenols present in fruit, vegetables, and whole-grain cereals), antibiotics, prebiotics, and/or probiotics.[105–107] Such possibilities have also been shown in interventional studies. Lam et al demonstrated that treatment with vancomycin, a very poorly absorbable antibiotic, led to a 27% reduction in myocardial infarction occurrence.[108] This effect was associated with a change in the gut microbiota at both the bacterial and fungal levels and a reduction in plasma levels of leptin (acting as a proatherogenic adipokine). The latter datum was confirmed in practice by the administration of leptin-suppressing probiotic *Lactobacillus plantarum 299v*,

which resulted in a 29% reduction in myocardial infarction in rats.[108] In a randomized controlled trial by Rajkumar et al,[109] the probiotic (VSL#3) supplemented group had a significant reduction in total cholesterol, triglyceride, LDL, very-low-density lipoprotein (VLDL), and hs-CRP, increased HDL value, improved insulin sensitivity, and a favorable change in the composition of gut microbiota. In this study, the addition of omega-3 fatty acid to VSL#3 had a more pronounced effect on HDL, insulin sensitivity, and hs-CRP. However, a meta-analysis of clinical trials of antibiotic therapy in patients with CAD failed to demonstrate any benefit with regard to mortality or cardiovascular events in CAD patients.[5,93]

The Role of Local Bacterial Infection in the Pathogenesis of Peripheral Vascular Disease

The infectious agents may reach the vascular wall, for example, after a surgical or intravascular procedure (stent infection),[45,109–111] via the bloodstream or their continuation from adjacent tissues. The most prevalent sources of blood-transferred infection are periodontal bacteria (most frequently: *A. actinomycetemcomitans*, *P. gingivalis*, *P. intermedia*, and *Tannerella forsythia*) and an increased intestinal permeability.[12,18–20] The first report concerning the presence of bacteria causing periodontal diseases in atherosclerotic plaques appeared in 1999.[112] Gram-negative microorganisms living in dental plaque and periodontal pockets produce adhesins (fimbriae, pili, fibrils, and capsules), enzymes, toxins, and many other metabolites, which, in direct or intermediate ways, lead to damage of the connective tissue and bones of the alveolar process. Different dental procedures, and even chewing and tooth brushing, may enable bacteria and their toxins and metabolic products to enter the bloodstream. The most prevalent bacteria causing periodontitis are *P. gingivalis*, *T. forsythia*, *P. intermedia*, *Prevotella nigrescens*, *A. actinomycetemcomitans*, *Treponema denticola*, *Fusobacterium nucleatum*, *Eikenella corrodens*, *Parvimonas micros*, and *Campylobacter rectus*. The presence of these microorganisms in atherosclerotic plaques has been proven using different laboratory methods, such as polymerase chain reaction (PCR), DNA hybridization, culture, and electron microscopy.[113]

Atherosclerotic plaque colonization by other microorganisms such as *Hp*, *C. pneumoniae*, or CMV, HIV, and mycobacteria has also been reported.[41,43,44,112–119] Through this pathway, a microorganism that reaches the vascular wall in the bloodstream and nestles in atherosclerotic plaques can stimulate inflammatory cells, contributing to cytokine overproduction and subsequently to local endothelial and vasomotor dysfunction, foam cell formation, smooth muscle cell proliferation, platelet aggregation, and cytokine production, as well as vascular remodeling impairment, for example, after peripheral artery angioplasty, stenting, or atherectomy.[7,120] Serra et al[121] found identical phylotypes in atheroma and subgingival samples in 17 of the 18 patients, indicating possible bacterial translocation between periodontal pockets and coronary arteries. The DNA, RNA (PCR analysis), and antigens of a variety of oral bacterial species (e.g., *P. gingivalis*, *A. actinomycetemcomitans*, *T. forsythia*, *F. nucleatum*, and *Streptococcus mutans*) have

been detected in atherosclerotic plaques in peripheral arteries.[7,26] Suzuki et al[26] showed that *P. gingivalis* affected the progression of abdominal aorta aneurysm through toll-like receptors (TLRs) and matrix metalloproteinases (MMPs). Figuero et al[122] demonstrated the presence of *A. actinomycetemcomitans* in vascular, blood, and subgingival samples in only 1 of the 36 patients, which, in the authors' opinion, in spite of its low frequency, supported the hypothesis of a translocation of periodontal pathogens from subgingival microbiota to the bloodstream and then to atheromatous plaques in carotid or other peripheral arteries. Kędzia et al[123] reported successful isolation of anaerobic periodontal bacteria from 68% of atherosclerotic plaques obtained from the carotid arteries of 37 patients. In the work by Rangé et al,[124] 73% of the carotid samples were positive for periodontal bacterial DNA. Moreover, in this article, intraplaque hemorrhage was present in 73 of the 157 (46%) carotid samples and was associated with neutrophil activation, reflected by the release of myeloperoxidase (MPO), cell-free DNA, and MPO-DNA complexes. In this study, lipopolysaccharide levels in a carotid medium were also linked to intraplaque hemorrhage but not with neutrophil activation markers.

The role of periodontal bacterial infection in the pathogenesis of peripheral artery arteriosclerosis has also been shown in animal models. Hokamura and Umemura,[125] although they state that detection of *P. gingivalis* in specimens from aneurysmal or atherosclerotic blood vessels from patients was markedly lower than that of other oral bacteria such as *S. mutans*, found that an intravenous administration of *P. gingivalis* induces intimal hyperplasia associated with overexpressions of S100A9 and SMemb in a mouse model with photochemical impairment of the femoral artery. The authors concluded that an upregulation of S100A9 by the oral-hematogenic spread of *P. gingivalis* may be one of the important events in the development of cardiovascular lesions, such as aneurysm, aortic hyperplasia, and atherosclerosis,[7,125] because such bacteremia is possible even, for example, during tooth brushing or after dental procedures, such as extractions, scaling, root planing, and periodontal surgery. In patients with periodontitis, Waghmare et al[126] observed *P. gingivalis* in 70% of the patients immediately after scaling and root planing, which had reduced to 25% after 30 minutes. Moreover, 7.5% of the patients presented with bacteremia before the procedures, which demonstrates how dangerous an unhealthy oral cavity can be. Suzuki el al[26] even suggested that periodontitis may have a greater effect on aneurysm progression than other cardiovascular diseases, although many aspects of these potential associations need to be clarified. In vitro studies have demonstrated that periodontal pathogens are able to infect endothelial cells, smooth muscle cells, and macrophages, eliciting the production of proinflammatory cytokines and chemokines (e.g., IL-6 and monocyte chemoattractant protein [MCP]-1) and the formation of foam cells, hence contributing to atherosclerosis.[7]

Other pathogens, not typically related to periodontitis, have also been found in atherosclerotic plaques. The role of *Hp* is still under debate concerning patients with chronic, stable CAD, as well as in the course of acute coronary syndromes.[5] The particular pathogenic role of *Hp* in atherosclerosis pathogenesis results from the possibility of VacA and CagA protein production, which makes some *Hp* strains more cytotoxic in terms of potential local vascular wall injury, as well as inducing greater stimulation of autoimmunological cross-reactions in the above-described mimicry interactions. The presence of *Hp* DNA in the coronary artery has been found by Kowalski et al,[43,44] Iriz et al,[114] Kilic et al,[116] Kaplan et al,[118] and Adiloglu et al.[119] However, Ahmadnia et al[127] did not confirm these observations. Kędzia et al[128] cultured *Hp* from 6.4% of the atherosclerotic plaques from femoral arteries and from 5% of the samples from the iliac arteries of 51 patients operated on due to lower limb ischemia. Kaplan et al[118] detected *C. pneumoniae* in 16 of the 52 patients (30.8%) and *Hp* DNA in 9 of the 52 patients (17.3%), and Ameriso et al[129] revealed *Hp* DNA in 20 of the 38 (53%) atherosclerotic plaques obtained during carotid endarterectomy.

However, other pathogens may also injure the vascular wall through direct action. Determann et al,[6] in a female patient suffering from right calf claudication caused by a short occlusion of the superficial femoral artery, found atheroma and atypical mycobacteria within adventitial caseating granulomata in a histological examination of an excised segment of the artery. *C. pneumoniae*, CMV, HCV, etc., may also act directly on the arterial wall, contributing to local endothelial dysfunction, foam cell formation, smooth muscle cell proliferation, platelet aggregation, as well as cytokine, reactive oxygen species, growth factors, and cellular adhesion molecule production.[7,130] The positive strand of HCV RNA has been detected in carotid plaque tissues from anti-HCV antibody-positive patients, but has not been found in anti-HCV antibody-negative patients. Chronic HCV infection has also been associated with vasculitis and mixed cryoglobulinemia, which may cause vascular injury as well as cerebrovascular damage.[7] In addition, infection with VZV may induce vasculopathy, which can cause ischemic infarction of the brain and spinal cord, as well as aneurysm, subarachnoid and cerebral hemorrhage, and carotid dissection.[131] VZV vasculopathy in immunocompetent or immunocompromised individuals can be unifocal or multifocal, following a similar course as HIV vasculopathy with deep-seated and superficial infarctions.[132]

The Role of Bacterial Infection in the Pathogenesis of In-Stent Thrombosis and In-Stent Restenosis in Peripheral Vascular Disease

Microorganisms may affect stented vessels both through stent infection and augmentation of the processes leading to in-stent restenosis.[45,110,111] Stent infection is a very important but rare or underreported complication of intravascular procedures. This type of complication may occur during intervention and through bacteremia. *Staphylococcus aureus* is the most prevalent microorganism causing such complications. One potential clinical manifestation of stent infection may be the occurrence of fulminant coronary pseudoaneurysm.[110] One of the factors predisposing to stent infection is the implantation of sirolimus- and paclitaxel-eluting stents,

which, in contrast to bare metal stents (BMS), are more likely to present immunomodulating and antiproliferative effects.[110] Suspected bacterial stent infection should be managed aggressively. Antibiotics alone may not be sufficient, and many patients need a resection of the infected segment and a bypass surgery.

Bacterial infection may also lead to induction and/or acceleration of in-stent restenosis, which is a process mainly related to neointimal proliferation. It is induced by vascular wall injury during ballooning or stent implantation, and the release of platelet growth factors, such as PDGF, and thrombin activation. The neointima is mainly constituted of VSMCs of subjacent medial origin. During their migration and intimal proliferation, VSMCs partially lose their contractile phenotype and acquire a synthetic one.[14] The role of bacterial infection in restenosis process activation has been shown in the work by Kowalski et al.[44] These authors revealed the presence of *Hp*-specific DNA in atherosclerotic lesions in patients with CAD and a greater mean coronary artery lumen loss (in-stent restenosis) 6 months after percutaneous coronary intervention in patients infected by CagA-positive *Hp* strains in comparison with *Hp* IgG-positive but CagA-negative and *Hp*-seronegative patients.

Recognition of the role of bacterial infection in the pathogenesis of restenosis shows potential opportunities for therapeutic targeting with arterial remodeling.[133] *C. pneumoniae* infection could play an important role in the mechanisms of restenosis,[111,134] and, because rapamycin can inhibit its growth effectively, the use of this antibiotic in rapamycin-eluting stents as an immunosuppressive and antiproliferative drug should prevent neointima formation and reduce the risk of in-stent restenosis.[111] On the contrary, such observations would support the hypothesis regarding the role of infectious agents in the pathogenesis of in-stent restenosis, which concerns not only coronary, but also peripheral artery stents. Other potential interventions in preventing infection-induced in-stent restenosis might be the use of a drug-coated balloon or a perivascular injection of antibiotics following bypass surgery or endarterectomy.[133]

Bacterial Infection and Venous Diseases

Systemic infection can lead not only to arterial disorders but also to venous diseases. The most frequently suggested link between infection and venous diseases is acquired thrombophilia, resulting from an increase of coagulation factors in the blood, as an effect of an acute phase reaction (e.g., factor VIII and fibrinogen). Han et al[135] also found that periodontal pathogens may induce anticardiolipin and other antiphospholipid antibodies in patients with periodontitis by molecular mimicry of the serum protein β-2 glycoprotein. The most prevalent clinical manifestation of such associations is venous thromboembolic disease. However, recent publications present the possibility of such associations through the mechanism of vascular wall injury by local as well as systemic inflammatory disease. Examples of such associations are given in case reports showing the occurrence of deep vein thrombosis in the course of perivascular tissue inflammation,[13] portal vein thrombosis in patients infected by CMV,[130] and HIV,[132] as well as life-threatening intracranial and internal jugular vein thrombosis caused by common ear, nose, and throat (ENT) infections.[136] The vascular surrounding tissue (PVAT mainly) was also reported as being important for saphenous vein graft patency in pioneer human studies.[13]

Conclusion

The relationships between bacterial infection and pathogenesis of peripheral atherosclerotic vascular disease potentially have several aspects of an epidemiological, pathophysiological (bacterium and host interplay), and therapeutic nature (e.g., rapamycin-eluting stents). However, in spite of numerous data, the role of bacterial infection in the course of PAD still remains controversial and requires randomized, controlled trials to evaluate its true relevance, particularly with respect to the outcome of bacterial eradication for the risk of PAD progression, stent thrombosis, in-stent restenosis, as well as hard clinical endpoints. Long-term observational studies are also needed to identify the role of the host age in the pathogenesis of infection-induced and accelerated PAD. The role of active or past infection in respect to peripheral artery atherosclerosis complications, especially cerebrovascular, should also be investigated.

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