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REVIEW ARTICLE

Periodontitis as a risk factor for cardiovascular disease: The role of anti-phosphorylcholine and anti-cardiolipin antibodies

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Abstract

Available evidence does allow an interpretation of periodontitis as being a risk factor for atherosclerosis and coronary heart disease. There is now a convincing body of evidence that mechanism of atherosclerosis has a major inflammatory component and it is much more than the simple accumulation of lipids on the vascular walls. Studies have shown that certain other mild bacterial infections consist a major risk factor for stroke in young and middle aged patients. Several possible mechanisms could explain the observed association between infection and infraction. The evidence supports the premise that periodontitis leads to systemic exposure to oral bacteria and that the resulting production of inflammatory mediators is capable of initiating or supporting mechanisms associated to development of atherosclerosis and coronary heart disease.

Studies in patients with pathologic concentrations of anti-cardiolipin and anti-phosphorylcholine antibodies demonstrated increased pocket depth and attachment loss, compared to patients with normal levels of the above antibodies. These antibodies could be associated to increased risk for stroke and atherosclerosis in patients with periodontitis.

As we become more familiar to the association between periodontitis and cardiovascular disease it is likely that in the future periodontal disease may be added to the list of the factors which are used to assess patients' risk profile for coronary heart disease and stroke. Hippokratia 2008; 12 (3): 144-149

Key words: periodontitis, infection, infraction, cardiolipin, phosphorylcholine

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Cardiovascular disease occurs as a result of a complex set of genetic and environmental factors[1-4]. The genetic factors include age, hypertension[5], diabetes[6], marked obesity[7], lipid metabolism[8], fibrinogen levels[9,10] and platelet P1 polymorphism[11]. The environmental risk factors include diet[12], physical inactivity, stress[13,14], cigarette smoking[15,16], socioeconomic status[17], chronic infections[18,19], use of non-steroid anti-inflammatory drugs[20] and possible endothelial cell injury[21-23]. Cardiovascular mortality rates account for about 30% of all deaths, despite efforts aiming at controlling the conventional risk factors. The identification of factors leading to an increased risk of coronary heard disease is still far from complete. It has been estimated that, to a significant percentage of patients with the disease, no one of the established risk factors aforementioned, does apply[24].

Periodontitis is an inflammatory disease of the gums, which affects all the dental supporting tissues. It has been mentioned that severe generalized periodontal disease is present in 8% to 13% of the world's adult population[25,26]. The prevalence is lower in children and young adults with an estimated rate 2% to 5% between the ages of 11 and 25 being affected[27]. Periodontitis is a progressive inflammation, leading to the destruction of the supporting tissue and alveolar bone loss[28,29]. This process is the result of the bacteria – produced toxins and the inflammatory reaction of the gum tissues[30].

Today, the available evidence does allow us an interpretation of periodontitis being a risk factor for atherosclerosis coronary heart disease[31].

In this paper, we examine the evidence for an association between periodontal infections and increased risk of cardiovascular disease and we also study the connection between periodontal infections and increased concentration of antiphosphorylcholine and anticardiolipin atnibodies in the serum of patients with periodontitis.

Infection, inflammation and atherosclerosis

Infection has been recognized for decades as a risk factor for atherogenesis and thromboembolic events[32-35]. Gram-negative bacteria or the associated lipopolysaccharide (LPS) endotoxin, when presented as a systemic challenge in animal models, can induce inflammatory cell infiltration into major blood vessels, vascular smooth muscle proliferation, vascular fatty degeneration and intravascular coagulation[32-36]. The remarkable similarities of bacteria-induced vascular pathology and the natural history of atherogenesis has to investigators to suggest that, infections of unknown origin may contribute to the observed cardiovascular pathology in addition to genetic and dietary influ-

ences[32-39]. It has, already, been suggested the association of certain infections with atherogenesis and thromboembolic events as risk factors for this condition[31].

The association with increased coronary heart disease and stroke risk is strongest for Chlamydia pneumoniae (Cp). Cp is believed to disseminate through the blood to infect the vascular endothelium and contribute to the occurrence of atherosclerosis[38,39]. As shown by immunofluorescent techniques, antigens of Cp localize to atherosclerotic plaques with a high prevalence in individuals with prior coronary bypass surgery. Control specimens of coronary arteries obtained from individuals without clinical signs of coronary artery disease rarely show evidence of Cp infection. Other microbes or viruses, which are implicated in the pathology of atherosclerosis, include Helicobacter pylori[38], cytomegalovirus[40-42], and Herpes virus type 2[43].

Helicobacter pylori, which is known for its colonization on gastric mucosa, has been related with increased risk of coronary heart disease[44]. It has been found that there is a 33% prevalence of antibody reactive with β2GPI in patients with Helicobacter pylori infection[45]. Other bacterial infections that may trigger the production of these antibodies range from spirochetes infections such as Syphilis and Lyme disease to those involving non-periodontal Staphylococcal and Streptococcal organisms[46].

As atherosclerotic lesions develop in the coronary arteries, the risk for occurrence of myocardial ischemia and infraction increases[47].

Possible role of dental infections in the etiopathogenesis of atherosclerosis, coronary heart disease and stroke

Oral flora is normally confined in the mouth, located on the surfaces of the tongue, gingiva, mucous membranes and teeth. Periodontal pathogens, invade epithelial cells and connective tissue causing periodontal inflammation and bleeding which enables entry of oral flora, including non-invasive organism, into the blood stream and transportation to systemic locales. Procedures such as dental extraction, periodontal surgery, tooth scaling and even the brushing of teeth often lead to the presence of oral bacteria in the blood stream (bacteremia). There is evidence that common oral hygiene practices daily produce low-level bacteremia[48].

Certain oral bacteria are known as causative agents associated to infective endocarditis[49,50]. Furthermore, dental bacteremias associated to periodontitis are considered as risk factors for coronary heart disease and stroke[51].

Atherosclerotic plaque samples are often found infected with multiple infectious agents, as Porphyromonas gingivalis and Sstreptococcus sanguis, which are common in periodontal disease. The immunolocalization of these microorganisms within unstable plaque regions and their association with plaque ulceration, thrombosis and apoptosis in vascular cells, are intriguing. Multiple infectious agents may alter vascular cell function and provide the possibility for acute ischemic stroke events[51].

Streptococcus sanguis is the most prevalent species in dental plaque[52] and frequently identified in the polymicrobial bacteremia form dental foci[53]. Platelet aggregating strains (Agg+) of Streptococcus sanguis are found to induce aggregation of human platelets in vitro[54-56]. This phenomenon is mediated by the expression of the platelet aggregation-associated protein (PAAP) on the surface of certain strains[57]. The PAAP is a collagen-like cell surface antigen containing the sequence KPGEPGK[58]. This sequence forms a structural motif common in all known platelet-interactive domains of collagens[59-61].

In experimental studies on rabbits, PAAP was found to induce the formation of platelet vegetation during endocarditis[62]. Following infusion of Agg+ Streptococcus sanguis, platelets and fibrin accumulation on injured heart valves, was observed[56]. To verify that valvular vegetation was indeed thrombi, rabbits were treated to inhibit formation of digest platelet-associated fibrin[63]. The eventual mass of the vegetation was reduced by pretreatment with monospecific rabbit antifebrin antibody or by therapy with recombinant human tissue plasminogen activator.

When present in the circulation, Agg+ Streptococcus sanguis may also induce thromboembolic events. The Agg+ phenotype may be associated with the occurrence of disseminated intravascular coagulation-like syndrome in immunocompromised patients[64,65]. Approximately 60% of human isolates express the Agg+ phenotype[66]. Studies have shown that infusion of Agg+ colony strains causes a rise in blood pressure, heart rate, increased cardiac contractility and chances in electrocardiograms (ECGs) in rabbits[58,67].

Inflammatory cells and the inflammatory mediators such as tumor necrosis factor alpha (TNF-α), interleukin-1 beta (IL-1β) and prostaglandin E2 (PGE2) play a key role in human coronary heart disease and atherosclerosis[36,68-70]. Bacterial LPS initiates the expression of IL-1b, which impedes fibrilonysis but facilitates coagulation and thrombosis[71]. Cytokines enhance both cholesterol accumulation in monocytes and smooth muscle proliferation, which presumably results in thickening of vessel walls[36,64]. Thus, the pathway LPS, moncyte activation, inflammatory-mediator production is implicated as an important mechanism in the pathogenesis of coronary heart disease and atherosclerosis. Today, the existence of inflammatory response in the process of the periodontal disease has been proved[72]. Monocytes within the periodontal tissues respond to LPS production of the plaque organisms by secreting important pro-inflammatory mediators, such as TNF-α, IL-1b, PGE2, and thromboxane A2 (TxA2), which not only cause local effects in the periodontal tissues, but may appear systemically[9,68]. Periodontal disease, like ischemic heart disease involves the above shown pathway[31]. The systemic response to oral pathogens is a result of bacterial penetration into tissues, loss of integrity of the epithelium in the periodontal sulcus and transient dental bacteremia. It has been shown that endotoxins of plaque microorganisms are capable of penetrating the gingival tissues and entering into the blood stream, in amounts sufficient to bring about a systemic LPS-specific antibody response[73].

The role of antiphosphorylcholine and anticardiolipin antibodies in serum of patients with periodontitis

Periodontitis is considered to be the result of the bacteria-host interaction[30]. A vital component of the etiology of periodontitis is the lipopolysacharite, located on the outer membrane of Gram-negative periodontal bacteria. This molecule has 3 major component parts: the core, the external O-antigen and the lipid A which is embedded within the lipid portion of the outer membrane[74] and is responsible for the endotoxin properties. Minor lippopolysaccharide antigenic components have also been identified. One such molecule is phosphorylcholine that is attached to cell wall polysaccharide and lipoteichoid acid[75] which has been identified in over 30% of the supragingival and subgingival flora, including Streptococcus oralis, Sterptococcus sanguis, Actinomyces israelii, Actinomyces naeslundii, Fussobacterium mucleatum, Haemophilus aphrophilus and Actinobacillus actinomycetemcomitans[76,77]. The possible function of phoshporylcholine is that certain bacteria may utilize it to gain access to endothelial cells[78] or the circulation[79-81]. Bacterial adherence, colonization and invasion are reliant upon surface phosphorylcholine. It has been shown that Streptococcus pneumoniae and Actinobacillus actinomycetemconimans invasion into endothelial cells is based on the interaction between surface phosphorylcholine and endothelial surface receptors for platelet activating factor[79,80]. Phosphorylcholine, as a component of the lipopolysaccharide (LPS) motive of many bacteria, plays a role in prompting a host immune response. Studies have shown that Phosphorylcholine influences polyclonal B-cell differentiation and activation[82,83]. Additionally, there is host production of IgG and IgM antibodies directed against Phosphorylcholine, which can assist to monocyte recognition and phagocystosis of the pathogenic bacteria. Phosphorylcholine - positive strains of Streptococcus pneumoniae and Actinobacillus actinomycetemconimans become opsonized by anti-phosphorylcholine IgG[84]. Signs of such host-periodontal pathogen interplay are not only detected locally but also systemically. The ability of periodontal pathogen bacteria of producing a systemic response to phosphorylcholine is demonstrated by higher serum levels of antibodies directed toward phosphorylcholine (anti-phosphorylcholine IgG) in patients with attachment loss, in comparison with those with healthy gums[76]. Furthermore, other researchers suggest that both phosphorylcholine bearing strains of oral bacteria and oxidized low-density lipoproteins (oxLDL) react with anti-phosphorylcholine IgG from human serum[85]. This suggests that antibodies produced against certain periodontal bacteria would also react to phosphorylcholine-bearing oxLDL[86] and, therefore, magnify the uptake of this lipid by foam cells, promoting further progress of atherosclerosis.

Cardiolipin (CL) is a phospholipid found in mammalian tissues and eukaryotic organisms and is also produced by some prokaryotic bacteria. It is located in the inner mitochondrial membrane and it is suggested that it plays an integral role in normal electron transport and energy metabolism[87].

Antiphospholipid antibodies consist a group of autoantibodies found in several pathologic conditions, including a variety of infectious diseases and are a hallmark of the anti-phospholipid syndrome (APS). APS is present in about 30 to 40% of patients with systematic lupus erythimatosus (SLE), although there are individuals with the primary form of APS, which do not develop SLE. The major clinical symptoms of APS include recurrent venous or arterial thrombosis and fetal loss. Patients with APS may also demonstrate premature atherosclerosis. Pathogenesis of APS is related to prothrombotic activity of some antiphoshpolipid antibodies[88]. Among the major groups of antibodies detected in patients with APS are b-2glycoprotein, I-dependent anti-cardiolipin (anti-CL), anti-β-2glycoprotien I (anti-β2GPI) and lupus anticoagulant (LA). β2GPI is a 50kDa plasma phoshpolipid-binding protein which functions as a natural anticoagulant[89]. Immunoassays measuring pathogenic anti-CL require the incorporation of β2GPI bound to CL for detection of anti-CL autoantibodies that promote procoaguland activity[90,91]. Autoantibodies directed at β2GPI may also be detected in immunoassays that omit CL, though these subsets of anti-CL and anti-β2GPI may not be identical[92]. In summary, this group of antibodies is heterogeneous and clinical tests usually involve multiple assays to detect autoimmune anti-CL and anti- β2GPI.

Recent studies strongly implicate bacterial and viral infection in the etiology of APS due to induction of cross-reactivity anti-CL autoantibodies. A hexapeptide (TLRVYK) sequence in β2GPI has been identified to be recognized by some anti- β2GPI monoclonal antibodies. Mice immunized with microbial pathogens such as Hemophilus influenza or Neisseria gonorrheae with homologous sequences related to TLRVYK, produced cross-reactive anti- β2GPI that induced APS-like symptoms, when subsequently purified and passively infused into mice. Thus, bacterial infection could lead to production of pathogenic anti-CL and be responsible for a subset of cases of APS[93].

Periodontal bacteria including Actiobacillus actinomycetemcomitans, Porphyromonas gingivalis have been found to contain a peptide sequence similar to that on the β2GPI molecule[93-95]. In addition, there is evidence that β2GPI by itself is immunogenic[94], possibly compounding this response.

There are more examples suggesting an association between periodontitis and cardiolipin. Reports have demonstrated that the prevalence of patients with chronic periodontitis and generalized aggressive periodontitis positive for anti-CL autoantibodies was greater than in healthy controls and patients with localized aggressive periodontitis. Patients with elevated anticardiolipin had greater mean attachment loss and increased pocket depth[96].

A recent clinical study in patients with aggressive periodontitis has observed an association between sys-

temic vascular inflammation markers and elevated levels of anti-CL[97].

Conclusions

Epidemiological data indicate that periodontal disease is an independent risk factor for myocardial infarction. Periodontal infections have also been suggested as one of the several factors contributing to the development of coronary heart disease[98]. Evidence supporting a causative role of chronic infection in coronary heart disease is largely circumstantial.

The evidence supports the premise that periodontitis leads to systemic exposure to oral bacteria and that a potential source of systemic inflammatory mediators, capable of initiating or worsening conditions associated with atherosclerosis and coronary heart disease, are cytokines and LPS produced in the infected periodontal tissues, which enter into the blood stream. Cytokines produce their effects directly, whereas the LPS trigger a systemic cascade of inflammatory cytokines, also capable of eliciting effects associated with atherosclerosis and coronary heart disease.

The continued systemic exposure to Gram negative bacteria and LPS results in a release of cytokines such as tumor necrosis factor alpha (TNF-α), interleukin-1 beta (IL-1β) and prostaglandin E2 (PGE2) which may be a significant factor in the pathogenesis of coronary heart disease and stroke.

The suggestion that periodontal disease is a significant risk factor for coronary disease adds a new perspective to oral health and should serve to align it with the other aspects of preventive medicine. It also raises a core question about the effect of periodontal treatment in reducing the risk of heart disease.

Clinical studies on periodontal disease have revealed a positive association with coronary disease and emphasis is now being placed on understanding the relation between periodontal disease and atherosclerosis. It has already been demonstrated that anti-phosphorylcholine directed from pathogenic bacteria in the periodontal pocket may cause a cross-reaction with oxLDL, leading to events that culminate in atherosclerotic plaque formation.

As IgG anticardiolipin is a potential factor in atherosclerotic plaque formation and thrombosis, its association to periodontal bacteria becomes an important issue.

Patients with elevated anticardiolipin antibodies present greater mean attachment loss and increased pocket depth. It appears that the development of periodontitis demonstrating greater extent and severity may lead to the production of anticardiolipin antibodies in those patients.

It is likely that in the future periodontal disease may be added to the list of factors, which are used to assess patients' risk profiles for coronary heart disease and stroke. In addition, treatment of periodontal disease should become a standard part of the therapy for patients with the above diseases.

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