

Periodontitis, Bacteremia and Infective Endocarditis: A Review Study

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Abstract

Context: Earlier evidences show that periodontitis with inflamed and ulcerated crevicular or pocket epithelium surrounding the teeth may be a portal of entry for bacteria into the bloodstream. A newly proposed causal model predicts that an early bacteremia may affect the endothelial surface of the heart over many years and promote valve thickening rendering the heart valve susceptible to vegetation by a later bacteremia that would culminate over a few weeks into fulminant infection.

Evidence Acquisition: In this review, various published sources of information pertaining to periodontitis, bacteremia and infective endocarditis were reviewed. This review is focused on the role of the viridans group streptococci (VGS) in periodontitis, bacteremia and infective endocarditis.

Results: The viridans group streptococci present in the oral cavity were the most important causes of bacteremia following dental procedures and infective endocarditis. In most of the studies, significantly higher rates of bacteremia occurring in patients with periodontitis than patients without periodontitis indicated that periodontitis opens up the route for oral streptococci to gain entry into the bloodstream. In addition, the significantly higher rates of isolation of the VGS from the patients of infective endocarditis with periodontitis showed that there was a positive association between periodontitis, infective endocarditis and the VGS.

Conclusions: The literature survey presented in this review suggests that there is a definite relation between periodontitis, bacteremia and infective endocarditis and would provide valuable data for the future dentists as well as the physicians, because a large proportion of the world's population lives a lifetime with periodontitis. Moreover, infective endocarditis still remains a cause of concern as this disease is a cause of considerable morbidity and mortality regardless of modern antimicrobial and surgical treatment.

Keywords: Periodontitis, Viridans Group Streptococci, Bacteremia, Infective Endocarditis

1. Context

Periodontitis is a chronic inflammatory disease associated with destruction of connective tissue of gingiva, periodontal ligament and alveolar bone following untreated or improperly treated gingivitis (1). Bacterial biofilms (dental plaque) predominantly composed of the viridans group streptococci (VGS) are the primary etiological factors for the inflammatory process of gingiva leading to subsequent destruction of periodontal tissues (2). Loe et al. (1965) and Theilade et al. (1966) demonstrated that withdrawal of tooth brushing results in formation of plaque on the teeth and causes gingivitis in periodontally healthy individuals within 10 - 21 days (3, 4). Periodontitis is most commonly seen in adults and occasionally found in children.

Periodontitis induced inflammation may promote the oral VGS to gain access into the blood stream and eventually to the heart, resulting in the development of cardiovascular ailment such as infective endocarditis. There are several reports which have shown that the viridans streptococci are the most common cause of infective endocarditis

(5, 6) and the viridans group streptococcal bacteremia is more frequently inducible in patients with severe periodontal disease (7, 8). However, there are no reports on the collective analysis of the oral VGS and its relation with infective endocarditis in cases of periodontitis.

In the light of the emerging scientific evidences, questioning the role of VGS as oral commensal. A better understanding of the distribution of viridans streptococci in the dental plaque and its role in oral induced bacteremia, periodontitis and infective endocarditis needs to be investigated.

A comprehensive analysis of the VGS and its relation to the oral inflammatory disease like periodontitis and systemic diseases like infective endocarditis would provide a clear understanding of the periodontitis-infective endocarditis relationship, which may assist health care providers in their efforts to detect both of the diseases earlier. Gingivitis and periodontitis are treatable and preventable conditions; therefore, their identification as risk factors for infective endocarditis would have a major impact on infective endocarditis prevention.

2. Pathogenesis

Periodontitis is initiated as a simple marginal gingivitis, which further progresses to ulceration of crevicular epithelium. It proliferates further and gradually involves deeper portions of the periodontium leading to the advance lesion of the periodontitis. Gingivitis induced by the VGS and other bacteria in dental plaque, leads to the gingival inflammation caused by organisms present at the gingival margin (9). In the early stages, the supragingival bacterial plaque contains primarily Gram-positive aerobic bacteria, predominantly the VGS. Subsequently this composition changes to a more anaerobic, Gram-negative flora, which increases in time (10). An inflammatory response to this microbial challenge is mounted by the host leading to increased flow of the gingival crevicular fluid. Associated clinical changes involve increased edema, reddening and an increased tendency to bleeding in response to mechanical probing. The development and progression of plaque-induced gingival inflammation can be influenced substantially by systemic factors, both inherited and related to the environment (11).

Periodontitis results from a chronic inflammatory response to the subgingival bacteria (12). The main causative factor is the formation of a microbial biofilm predominantly composed of VGS, at the gingivocrevicular margin, which evokes an inflammatory response in the gingival tissue and progresses deeper into the periodontal tissue (13). Oral bacteria including the VGS, gather and coaggregate in colonies on the tooth surface, first supragingivally and thereafter subgingivally. With time, Gram-negative anaerobic microorganisms become more prevalent in the subgingival plaque, thereby enhancing its pathogenicity (14). The “red complex” that appears later in connection with the development of the biofilm consists of species of periodontal pathogens, such as, *Porphyromonas gingivalis*, *Treponema denticola* and *Tannerella forsythensis*, which occur more commonly in deeper tissue (10).

The mechanisms underlying the progression of gingivitis into periodontitis have not yet been established. Possibly, the bacteria themselves and/or their products (e.g., lipopolysaccharides-bacterial endotoxin) acquire the ability to penetrate deeper into the connective tissue, and/or perturbation of the host defenses allows deeper penetration (15).

The ecological plaque theory proposes that the increasing quantity of plaque provides an appropriate environment for colonization by and growth of more pathogenic bacteria (16). In this manner, the inflammatory response results in subgingival environmental changes and alters the balance of the resident microflora, which changes the gingivally healthy situation to gingivitis. Bacteria then

move further through the junctional epithelium and into underlying tissues, thereby predisposing to periodontitis (17).

3. Periodontitis and Bacteremia

Periodontal infections are inflammatory diseases. These are caused by a bacterial biofilm (dental plaque) that affects the tissues surrounding the teeth. In gingivitis, the infection is generally limited to the gingiva and the condition is reversible by taking due care of oral hygiene. However, in periodontitis, the inflammation extends deeper into the tissues affecting the attachment apparatus of the tooth. The occurrence of gingivitis and moderate periodontitis is very common and their prevalence increases with age (9).

Inflammation of periodontal tissue leads to deepening of the gingival crevice and formation of periodontal pockets, acting as a reservoir for a large number of microorganisms. Periodontal infections affect the oral tissues, in addition bacteria may get entry into the bloodstream via ulcerated inflamed crevice and pocket epithelium, and the adjacent gingival microcirculation. Invasive dental procedures and normal daily activities, such as chewing and tooth brushing are the important predisposing factors for entry of microbes into bloodstream (7, 18-22). Bacteremia and low-grade inflammation because of periodontal infections may carry a risk for systemic conditions. It has been observed that periodontitis is one of the causes or consequences of developing atherosclerosis. Microorganisms or their products present in circulation may promote pathogenesis and enhance local inflammatory changes in vessel walls and thereby may promote process of clotting and clot formation (23). The periodontal disease has also been reported to be an important risk factor for nonhemorrhagic stroke (24). Several other studies have also found that there is the oral-systemic link in various conditions like infective endocarditis and cardiovascular diseases, premature low birth weight deliveries, and diabetes mellitus (25-27).

Studies have shown that smoking increases the frequency and severity of periodontal disease (26). Smoking is associated with poor oral hygiene and hence, smokers have increased accumulations of plaque, calculus and increase the susceptibility of the host to bacterial growth (26, 27). Smoking also influences the periodontal disease through a variety of systemic effects such as decreased chemotaxis and phagocytosis by both oral and peripheral neutrophils, and reduced antibody production, which enhances the breakdown of periodontal tissues in smokers. As a result, smokers with chronic periodontitis have more attachment and bone loss, more furcation involvement

and deeper pockets, consequently smoking may enhance periodontitis induced bacteremia (28-32).

Most of the earlier studies show that inflamed and ulcerated crevicular or pocket epithelium around the teeth in patients with periodontitis may act as a portal of entry for bacteria into the bloodstream. In a study by Lockhart et al. (18), it has been observed that gingival bleeding after tooth brushing is associated with an almost eight-fold increase in risk of bacteremia. The incidence and the magnitude of bacteremia that occurs following chewing, tooth brushing, and invasive dental procedures are associated with gingival inflammation rather than with pocket depths (19). Bacteremia originating from the oral cavity is caused by a wide variety of microorganisms, including Gram-negative anaerobes and the VGS (17).

In many earlier studies, It has been found that the incidence and magnitude of bacteremia in patients with the periodontal disease are higher than those with a healthy periodontium (8, 19, 33). It has been reported that among patients with chronic periodontitis, the magnitude of bacteremia was directly associated with the level of gingival inflammation. However, there was no relationship found between probing depth and the magnitude of bacteremia, indicating that active inflammation was more important than periodontal attachment loss (19).

4. Bacteremia and Viridans Group Streptococci

It is a well-known fact that the oral cavity is the most likely origin of bacteremia due to the presence of the VGS in the oral cavity. *Streptococcus mitis* and *Streptococcus oralis* are the most common VGS found in the oral cavity, particularly in the setting of ulcerative oral mucositis (34, 35).

In 1978, studies in the United States produced the first report of the viridans streptococcal bacteremia. Hoecker et al. (1978) described six children in whom *S. salivarius* bacteremia was diagnosed. Their ages ranged from 6 - 14 years. The most common routes of entry were the mouth, pharynx or respiratory tract. Three patients, who were profoundly neutropenic, died in spite of antibiotic treatment with intravenous penicillin. The "penicillin G was found to be the antibiotic of choice in treating infections due to *S. salivarius*" and found that "these organisms were sensitive to the majority of antibiotics except aminoglycosides and tetracycline occasionally" (27).

In the 1980s, reports from other centers followed. In the U. K., Cohen et al. (1983) (35) evoked considerable interest and prompted groups elsewhere in Europe as well as in North America, to describe their recent clinical experience of the viridans streptococcal sepsis (28, 36). Substantial morbidity and mortality associated with a severe

form of the viridans streptococcal bacteremia became documented with complications such as septic shock and an acute respiratory distress syndrome (35, 36). In certain cases, in spite of the use of appropriate antibiotics, high mortality rates were associated with the severe form of the viridans streptococcal sepsis (35). During the 1980s, several studies described the viridans streptococcal bacteremia and a predominance of Gram-positive organisms in bacteremia patients, with the main organisms responsible, being coagulase-negative staphylococci, *Staphylococcus aureus*, and *viridans streptococci* (36). Identification schemes used in these studies suggested that *S. mitis* and *S. sanguis* were the most common species of the viridans streptococci causing bacteremia (35, 36).

In a study by Tomas et al. (2007), the prevalence of bacteremia following dental extractions was 96.2% at 30 seconds, 64.2% at 15 minutes and 20% at 1 hour after completing the surgical procedure. The bacteria most frequently identified in the positive blood cultures were viridans streptococci (63.8%) (32). During the early 1990s, studies on risk factors for viridans streptococcal and some case control studies were carried out (37, 38). Several studies associated the prophylactic use of certain antimicrobial agents, with the development of viridans streptococcal bacteremia (37, 39).

The majority of studies published at the beginning of the 1990s suggested that *S. mitis* and *S. sanguis* were the predominant species causing the viridans streptococcal bacteremia (39, 40). However, two groups of investigators found a different pattern. McWhinney et al. identified 47 sequential blood culture isolates of viridans streptococci from febrile patients (41) according to the scheme described by Beighton et al. (42) and also using the commercial system, API 20 Strep (bioMerieux). The former system, which accommodated the recent taxonomic changes of that time, identified 39 isolates of *S. oralis*, five of *S. mitis* and one of *S. parasanguis*. Two isolates could not be identified to the species level. One year later, the report by Beighton et al. using the same two identification schemes, also demonstrated that the more modern and comprehensive system identified *S. oralis* as the predominant strain (43).

Vergis et al. (2001) reported a decrease in bacteremia after dental extraction in 60% cases, who received prophylactic amoxicillin and in 89% cases who received no prophylaxis ($P = 0.30$), but their results were not statistically significant (44). Rajasuo et al. (2004) found that the detectable bacteremia at 10, 15, and 30 minutes were 44%, 25%, and 13%, respectively. Most prevalent aerobes were VGS and the *Streptococcus milleri* group (45). The world literature on the incidence of bacteremia after dental extraction shows that the incidence of bacteremia varies from 13% to 96%

and the incidence of bacteremia appears to be influenced positively by the presence of gingivitis, periodontitis, and other odontogenic infections (46).

5. Infective Endocarditis

Infective endocarditis (IE) is a severe disease that may affect one or more of the aortic, mitral, tricuspid valves but seldom the pulmonary valve. Preexisting valve diseases such as mitral valve prolapse (47), rheumatic fever, mitral stenosis, aortic stenosis (48) and aortic regurgitation, bicuspid aortic valve (45), coarctation of the aorta, previous endocarditis, prosthetic heart valves, and intravenous drug use are predisposing factors (49-53).

The viridans group streptococci have earlier been reported as the most frequent agents in IE. Kanafani et al. (2002) reported positive blood cultures in 77.5% of IE cases. *Streptococcus* spp. (51%; of which 57% were viridans streptococci) and *Staphylococcus* spp. (36%; of which 72% were *S. aureus* and 28% were coagulase-negative staphylococci) were the most commonly isolated organisms (54). In a study by Barrau et al. (2004), *Streptococcus* spp. were found to be associated with native valves, coagulase-negative staphylococci and *Coxiella burnetii* were associated with intracardiac prosthetic devices, and *S. bovis* and *S. aureus* were the predominant species associated with presumably healthy valves, whereas oral streptococci caused IE exclusively in patients with previous valve damage (55). Tariq et al. (2004) found VGS in 35% cases and staphylococci in 24% cases (56). Garg et al. (2005) reported streptococci in 23.2% cases, staphylococci in 19.7%, Gram-negative bacilli in 13.6%, enterococci in 8.1% and polymicrobial and fungal infections in 1.5% of IE cases (57). Nakatani et al. (2013) found that decayed teeth and periodontitis were the leading predisposing factors and VGS were isolated in 52% cases whereas, staphylococci were isolated from 32% cases (58).

In all, VGS are now the most frequent etiological agents in IE (54-61). Moreover, in nonintravenous users, where aortic or mitral IE dominates, VGS are the major etiological agents (25, 62). However, few studies have reported staphylococci to be the predominant isolates in IE cases (63, 64). These variations in frequency of isolation could be explained by differences in geographical regions as well as differences in patient populations. These reports show that rapid identification of the etiological agent is vital for successful management of the patient. Van Scoy demonstrated that patients who became afebrile in the first week of antibiotic therapy survived longer than those who remained febrile after the first week (61). *Staphylococcus aureus* is the most frequent etiological agent in IE among intravenous drug users, where the tricuspid valve is usually

affected, even if recent data have shown that the aortic or the mitral valve can be coinfecting (65).

Dental scaling and extraction lead to bacteremia in 70% - 100% (66) and tooth brushing leads to bacteremia in 40% of the children, where VGS were found in 50% of the cases (67, 68). Why VGS bacteremia in some cases leads to endocarditis depends on different factors. Old nonbacterial vegetation may be a predisposing factor in the valvular heart disease, a locus minoris (69, 70). Bacteria may infect the nonbacterial vegetations, which with adhesins attach to the endothelium of the damaged site on the valvular wall. Blood production of monocyte cytokines and other factors are parts of the pathogenesis (71). Bacterial components as dextran, fibronectin-binding protein and the teichoic acid have been described as important factors in adhesion to the platelet-fibrin matrix on the valvular wall contributing to the pathogenesis of IE (72). It is known that 60% of the *Streptococcus sanguinis* strains can cause platelet aggregation (73, 74), which is mediated by platelet aggregation-associated proteins (PAAP) (75). Activated platelets release dense and alpha granules, which in combination with thromboxane production play a role in the later aggregation response. Alpha granules include platelet microbicidal proteins (PMP) that kill bacteria; they also induce production of fibrinogen and clotting factors V and VII. The later activates thrombin, which initiates the polymerization of fibrinogen to fibrin (76). In earlier reports, dextran production by *Streptococcus sanguinis* has been reported to play a role in the pathogenesis of IE (73, 76); however, in another study it has been found that only 60% of the *Streptococcus sanguinis* strains produce dextran (77). Studies have showed that *Streptococcus gordonii* can attach fibronectin, which is adsorbed to collagen (78). The viridans group streptococci have glucosyltransferase (GTF), an enzyme using sucrose for synthesizing extracellular polysaccharide (79). The glucosyltransferase from VGS has been suggested as a factor forming biofilm on the surfaces of the teeth (80).

5.1. Viridans Streptococci and infective endocarditis

The threat posed by viridans streptococci is a consequence of their physical exodus from the oropharynx and skill in adapting to a new microenvironment. It is evident from various earlier studies that the oral cavity can act as the origin for the dissemination of bacteria to the heart; lungs and the peripheral blood capillary system, and this dissemination occurs in less than one minute after an oral procedure (81). The oral cavity has several barriers such as the surface epithelium, defensins, electrical barrier, antibody-forming cells, and the reticuloendothelial system (RES) to prevent bacterial penetration from dental plaque into the tissue (82). Those organisms involved

in transient bacteremia are usually eliminated by the RES within minutes and are generally asymptomatic to the host (81, 83).

A newly proposed causal model predicts that an early bacteremia may target the endothelial surface of the heart over many years and promote valve thickening thereby rendering the valve susceptible to adherence and colonization by a later bacteremia that would culminate over a few weeks into fulminant infection (6).

There are three steps critical for infection of the sterile vegetation leading up to IE pathology, these include bacterial adherence, platelet activation and fibrin overlaying. Microbial adhesion can be mediated by a variety of surface components and receptors, which act as virulence factors for the colonization of the endothelium. Adherence rates upon damaged aortic valve leaflets were measured from several species and it was found that *Enterococcus* spp. and viridans streptococci showed the highest rates of adherence than *Escherichia coli* (84). The ubiquitous presence of fibronectin on damaged tissue enables a surface binding protein, Fim A, to aid in colonization. Eighty percent of IE streptococci express this binding protein on the cell surface to reduce, ostensibly to coat the surface with the host protein and minimize a host immune response (85). Additionally, the streptococcal cell wall component, lipoteichoic acid (LTA), has been implicated as a fibronectin receptor (86).

More than 60% of *S. sanguinis* strains activate human platelets in vitro; this mechanism was elucidated by Herzberg et al. for this particular VGS member (76). The bacterial cell is thought to come into close proximity of the platelet via interaction between a cell surface adhesin (SsaB) and an unidentified ligand of the platelet. Platelet aggregation is stimulated by the action of the bacterial PAAP binding to the platelet $\alpha 2\beta 1$ integrin. An epitope on PAAP mimics the integrin's physiological ligands, collagen and von Willebrand factor, thus activates the platelet. The effect is morphological changes, surface expression of receptors for stimulators, followed by degranulation, results in release of clotting factors and fibrinogen. The resulting fibrin-platelet network increases in mass as cells colonize and expand layer upon layer of vegetation (87).

The newly colonized vegetation represents a unique biofilm environment that is surrounded by antimicrobial dangers. Planktonic cells, resulting from transient bacteremia or released from friable pieces of vegetation, will generally succumb to immune surveillance. The situation inside the fibrin barrier is quite different. Those organisms that can resist antimicrobial defence mechanisms multiply rapidly in the vegetation, soon reaching high numbers and then entering a stationary growth phase. As the vegetation enlarges, the colonies are gradually buried be-

low the accumulating layers and large numbers of cells (10^9 to 10^{15} per gram of tissue) are the consequence of the unimpeded thrombus growth (88). A phenomenon of sessile VGS biofilm communities is their ability to withstand host immune responses in regard to leukocyte access and impeded diffusion of materials compounded with slowed growth of the cells. The vegetation provides the bacteria with a "protected or privileged site" in which polymorphonuclear leukocytes penetrate poorly and are unable to check colony growth. Polymeric substances are known to retard the diffusion of antibiotics (89).

6. Conclusions

The results of the various earlier studies indicate that periodontitis is associated with increased incidence of bacteremia. In most of the studies, significantly higher rates of bacteremia were observed in patients with periodontitis than patients without periodontitis, indicating that periodontitis opens up the route for oral VGS to gain entry into bloodstream through the highly inflamed gingiva. Moreover, the higher rates of isolation of VGS from the patients of infective endocarditis with periodontitis support a positive association between periodontitis and infective endocarditis.

A clear understanding of this relationship between VGS, periodontitis associated bacteremia and infective endocarditis may help health-care providers in their efforts to detect both of the diseases earlier. Gingivitis and periodontitis are treatable and preventable conditions; therefore, their identification as risk factors for infective endocarditis would have a major impact on infective endocarditis prevention and assists in maintaining the optimal health of patients. However, large interventional studies can be performed to establish a causal relationship between periodontitis and infective endocarditis.

Footnotes

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