

# Periodontitis and Buerger's Disease: Recent Advances

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### ABSTRACT

Buerger's disease (BD) is a relatively rare thrombotic, occlusive and non-atherosclerotic clinical syndrome of unknown etiology. In recent years, numerous epidemiological studies confirmed the strong association

between chronic anaerobic periodontal infection and development of cardiovascular diseases, including BD. Therefore, the aim of this study is to clarify association between periodontal pathogens and Buerger's disease. Confirmation of presence and identification of periopathogens in patients with BD can

be considered crucial in developing novel therapies for BD. Further, periodontal therapy will lead to eventual improvement of BD patients' condition.

Key words: Buerger's disease; periodontal disease; thromboangiitis obliterans.

## 1. INTRODUCTION

Buerger's disease (BD), also known as thromboangiitis obliterans (TAO), is a relatively rare thrombotic, occlusive and non-atherosclerotic clinical syndrome of unknown etiology (1, 2). The disease was named after Leo Burger who gave a detailed description of the pathological findings of amputated gangrene limbs in patients with this disease (2). It is clinically seen as segmental vasculitis of small and medium-sized arteries and veins which may involve both arms and legs, particularly radicular and tibial arteries (1, 2). BD usually occurs in people around 40-45 years male heavy smokers (people who smoke one and a half packs of cigarette a day or more) and/or people who use any form of tobacco, such as cigars, chewing or snuffing tobacco and hand-rolled cigarettes using raw tobacco (3).

With the increase of tobacco use among women in the last 20 years, the incidence of BD in women rapidly grew (4). It is relatively rare in modern world and its prevalence is gradually decreasing over time, due to improvements in oral hygiene/dental care and strong smoke-free policies. Statistics are showing that BD is present 0.5 to 5.6% in Western Europe, 45 to 63% in India, 16 to 66% in Korea and Japan and 80% among Ashkenazi Jews (5).

It is present with the highest incidence in the Middle and Far East, where heavy

smoking is the most common (5). However, smoking alone, as environmental risk factor, does not seem enough to cause BD.

Several studies have suggested that BD is immune-mediated disorder, that is caused by cellular sensitivity to collagen and that BD susceptibility could be genetic (6, 7, 8, 9). Also an association between BD and the antiphospholipid syndrome, as well as hyperhomocysteinemia has been suggested (7). Additionally, some authors suggested strong seasonal variation for admission with winter admissions being significantly the most common (10).

The disease is characterized with coldness and pain in legs and arms (distal extremity ischemia) that decreases when stopping the activity (claudication) with inflammation, Raynaud's phenomenon and painful open sores on fingers and toes (gangrene). Since BD etiology and pathogenesis remained unknown, efficient therapy is lacking (1, 2).

The most effective way is to discontinue tobacco use completely, since even a few cigarettes a day can worsen the disease. Less effective treatments include medications to dilate blood vessels and improve blood flow, surgical sympathectomy to control pain and increase blood flow, therapeutic angiogenesis and terminally amputation due to gangrene (1, 2). Also use of hypnosis, as adjunctive therapy to standard medical treatments of advanced

BD was reported (11).

Periodontal disease/periodontitis is chronic inflammatory disease characterized by the destruction of connective tissue attachment and alveolar bone that might eventually lead to teeth loss. In recent years, numerous studies confirmed the strong association between chronic anaerobic periodontal infection and development of cardiovascular diseases, including BD (12, 13). However, the relationship between periodontitis and BD is not fully understood. Therefore, the aim of this study is to clarify association between periodontal pathogens and Buerger's disease.

## 2. MATERIALS AND METHODS

The articles published until March 2013 were obtained from the Medline/PubMed online database, using following search terms and key words: "Buerger's disease" AND "periodontitis", "thromboangiitis obliterans" AND "periodontitis", "periodontal disease", "Buerger's disease" and "periodontal bacteria". Secondary sources included papers cited by articles retrieved from the above mentioned studies.

## 3. RESULTS

Periodontal disease has been reported as a significant independent risk factor for BD mainly due to transit bacteremia, either directly through their cytotoxicity or indirectly by inducing or exacerbating

inflammation (14, 15). The oral cavity represents a potentially large reservoir of Gram-negative bacteria that are responsible for periodontal disease. Chewing food, flossing, tooth brushing and other mild traumas in persons with periodontitis might cause dissemination of periodontal bacteria through the systemic blood to infect and damage the vascular endothelium (15). Bacteremia will further cause aggregation, thrombi formation and a small arterial embolism (seen in the digital arteries by angiography). An inflamed periodontal tissue will release inflammatory mediators, such as interleukin-1 (IL-1), tumor necrosis factor-alpha (TNF- $\alpha$ ) and/or C-reactive protein (CRP) into the systemic circulation (12).

The main issue that can contribute to knowledge of association between periodontal disease and BD is identification of specific periodontal pathogens in peripheral arteries and veins (16). The presence of periodontal pathogens can be detected using quantitative polymerase chain reaction (Q-PCR). After confirmation of bacterial presence in the vascular lesions, their specific localization can be assessed by immunofluorescence (16). Among 300 species of periodontopathic bacteria (anaerobic bacilli and/or spirochetes) usually 7-8 bacterial species are considered and examined as representative ones, such as *Porphyromonas gingivalis* (*P.g.*), *Actinobacillus actinomycetemcomitans* (*A.a.*), *Prevotella intermedia*, *Prevotella nigrescens*, *Fusobacterium nucleatum*, *Campylobacter rectus*, *Treponema denticola* (*T.d.*), and *Tannerella forsythia* (*T.f.*; formerly *Bacteroides forsythus*/*Tannerella forsythensis*). So far periodontopathic bacterial DNA has been detected *in vivo* and clinically from carotid and coronary arterial plaques, abdominal aortic aneurysmal wall, atherosclerotic vessel plaques, primary varicose veins and from occluded arteries seen in BD (12, 22).

Regarding BD studies, Iwai et al. [9] performed PCR on 7 representative periodontal bacteria (*T.d.*, *A.a.*, *P.g.*, *T.f.*, *Prevotella intermedia* and *Campylobacter rectus*). They detected DNA of at least one species of periodontal bacteria in all oral samples (dental plaque and saliva samples) of patients with BD and in 13 of 14 arterial samples (9). While *T.d.* was found in 86% of arterial samples, other pathogens were found in 14-43% of the samples (9). To date, it has been reported that patients with BD exhibited high prevalence of se-

vere periodontitis with higher serum IgG titers against periodontal bacteria (*A.a.*, *T.d.*, *P.g.* and *Prevotella intermedia*) suggesting that periodontal infection may be associated with BD (9, 23). Further, the same research group found that the BD patients had increased titers of serum anti-cardiolipin antibody compared with healthy subjects (24). Similarly, using tissue specimens from anastomotic site of distal bypasses PCR, Chen et al. revealed the association. In the study periodontal bacteria (*P.g.*, *T.d.*, *A.a.* and *Prevotella intermedia*) were detected in 52% of specimens (25). Knowing that phlebitis migrans is present in 40% of BD patients, it is interesting finding that three out of four venous samples of phlebitis migrans showed presence of oral bacteria DNA (75%). Authors suggested that apart from arteries in BD patients, it is necessary to carefully observe veins, since they are also having some changes and damages accompanying BD (26).

#### 4. DISCUSSION

Interest in relationship of the periodontal disease and BD started 20 years ago and since then it has been studied extensively. So far, it is demonstrated that nearly two-thirds of patients with BD have severe periodontal disease. Periodontitis is associated with increased levels of C-reactive protein (CRP), glucose, fibrinogen and interleukin-18 (27). Therefore, decrease of periopathogens by periodontal therapy and/or periodontal surgery will eventually lead to systemic changes in some biochemical markers that are considered the risk factors for BD (28). Since BD is exclusively disease of heavy smokers, knowing smoking status will be a key parameter to assess periodontal and BD risk and therefore to make evidence-based clinical decisions. In order to reduce such risks, the need for interdisciplinary approach among physicians (e.g. cardiologists, family physicians, dentists/periodontists and nurses) is however necessary. The final aim of interdisciplinary approach is to optimize the periodontal conditions in patients with BD. Cardiologists should be obliged to explain the importance of periodontal health to BD patients and include periodontal therapy as an additional part of cardiovascular therapy. Our believe is that periodontal therapy might provide equal or even better outcome compared to standard treatments for cardiovascular diseases, including BD.

Since smoking cessation improves BD patient's dental and overall health condition, periodontists are also encouraged to take efforts in smoking cessation education and counseling as a part of standard periodontal therapy. An education of patients is very important for prophylaxis of all cardiovascular diseases, including BD. In countries where BD is very common, anti-smoking campaigns should give an accent on the education of children and youth in order to prevent smoking among that population. We believe that smoking cessation programs delivered in primary and specialty care settings, particularly of interdisciplinary team efforts may result in high health benefits at the population level.

Results from our study documented strong relationship between periodontitis and BD. However, the results should be interpreted with caution due to small number of studies published so far and difficulty in precise evaluation of the results, due to lack of appropriate investigations. The big concern is the fact that periodontal bacteria are anaerobes with no chances of long survival in oxygenized areas, such as arteries and veins. Therefore, it is almost impossible to cultivate *in vitro* periodontal bacteria obtained from arteries and veins. Also, it is well known that PCR does not provide evidence as to the bacteria's viability. It was recently suggested that *P.g.* and *A.a.* could invade host cells, suggesting their eventual viability (15). However, along with further clinical studies, supportive *in vitro* research would be necessary in order to further elucidate pathophysiology and relationship between BD and periodontal disease.

#### 5. CONCLUSION

Periodontopathic bacteria may play a significant role in the development of BD and may be considered as a therapeutic target in the prevention of BD expansion. Consequently, periodontal treatment would lead to an improvement of BD.

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