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EDITORIAL COMMENTARY

The role of periodontal microorganisms in the pathogenesis of myocardial infarction. From PCR techniques to Microbiome Sequencing.

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Periodontitis is an infectious disease that affects the tooth-supporting tissues and exhibits a wide range of clinical, microbiological, and immunological manifestations. It is associated with and probably caused by a multifaceted dynamic interaction among specific infectious agents, host immune responses, hazardous environmental exposure, and genetic propensity (1). Bacteria populating the tooth surface in form of a biofilm can infect the gingiva, which may trigger an immune response in gingival tissues. Pathogenic bacteria originating from the inflamed periodontium may penetrate into the body via the vascular system, either by entering the blood or lymph directly or as internalized particles of immune cells (2)**.** These oral pathogens, their toxins or their metabolic sub-products may enter into the systemic circulation and move to distant parts, initiating a distant disease (3). Oral bacteria play a role in various systemic conditions including atheromatous plaques and other cardiovascular diseases (4), and several periodontal pathogens (*Porphyromonas gingivalis*, *Treponema denticola* or *Fusobacterium nucleatum*) have been isolated in samples from cardiovascular patients (5). Therefore, it might be conceivable that prolonged inflammation, for example oral inflammation, increases the risk of cardiovascular secondary complications as it further elevates the already high inflammatory burden (6). Oral inflammation increased the circulating levels of many other inflammatory markers and cytokines in addition to C-reactive protein**,** are potent inducers of systemic inflammation which may increase inflammatory activity in existing atherosclerotic lesions, thereby increasing the risk of cardiovascular disease (7). At least four basic pathogenic mechanisms have been proposed that involve oral inflammation in the pathogenesis of atherosclerosis: (1) low level bacteremia by which oral bacteria enter the blood stream and invade the arterial wall; (2) systemic inflammation induced by inflammatory mediators released from the sites of the oral inflammation into the blood stream; (3) autoimmunity to host proteins caused by the host immune response to specific components of oral pathogens; (4) pro-atherogenic effects resulting from specific bacterial toxins that are produced by oral pathogenic bacteria. It is interesting to note that the detected bacterial species were not be limited to pathogenic species, such as *P. gingivalis*, but also included benign species that are generally associated with dental plaque on tooth surfaces (8). It can be assumed that higher abundance of periodontal pathogens the greater is the probability that these bacteria enter the circulation, with possible involvement of periodontal pathogens in the pathogenesis of atheromatous plaques (9).

Joshi et al. present a study in which they perform a systematic review on the prevalence of periodontal pathogens on authors of this systematic review have determined the prevalence of periodontal microorganisms in coronary atheroma plaques or clot samples collected from periodontal patients with myocardial infarction (10). They include 14 studies and perform a description their characteristics and a quantitative analysis of them. As indicated in the quantitative analyses, they found a high level of heterogeneity that could be related to a variety

factors, but essentially, they state that the main cause of heterogeneity were the different periodontitis case definitions and the differences in the microbial detection techniques among studies. They conclude that there is a consistent detection of periodontal pathogens in these samples, which is compatible with a potential dissemination of these bacterial species from the periodontal infected sites. They also highlight *P. gingivalis* and *A. actinomycetemcomitans* as the main prevalent periodontal microbes in atheroma plaques. However, it should be investigated whether they are merely bystanders or induce any structural changes within coronary arterial walls.

PCR-based techniques have been the main source of knowledge in periodontal microbiology in the last years. However, since the arrival of the concept of microbiome and the implementation of the sequencing techniques, new considerations have begun to arise in the current evidence on periodontal microbiology. The microbiota or human microbiome is the aggregate of microorganisms located in different places of the organism of healthy individuals. Under normal conditions, species of resident microorganisms in the oral are in balance with the host in a dynamic biological interaction. The long-term stable oral microbiome is the result of the microbiota maintained equilibrium, surviving to a daily variety of physical and chemical perturbations (11). It interacts with the mucosal immune system through a balanced equilibrium between symbiotic or pathogenic factors and the defense mechanisms of the immune system (12). When a disbalance in the oral microbiome occurs, appear the dysbiosis; allowing the bacteria to become pathogenic and cause diseases, such as caries and/or periodontal diseases, which could have a relevant impact on the general health (13).

The subgingival microbiome plays a key role in the pathogenesis of periodontitis. Multiple studies using 16S ribosomal RNA sequencing have identified the taxonomic composition of the subgingival microbiome in both periodontal and healthy individuals (14). But also, on peri-implantitis, a condition that affects the surrounding tissue of dental implants and that has some shared characteristics with periodontitis. Profiles of peri-implant microbiome have been found to be different between subjects and have also shown different compositions from the typical periodontitis profile. These results have shown that, although both diseases share some common clinical features, they could be caused by different microbiome profiles (15). Putative pathogens including mainly Gram-negative anaerobic bacteria, spirochetes but also viruses have been traditionally related to periodontitis through the results obtained by PCR techniques, with the obtention of mixed results sometimes that has not allowed to reach a consensus on the species that may cause the diseases. The debate on which species are particularly virulent and could lead to disease has lasted decades and is not resolved. However, it is probable that no single pathogen is causative on its own, but rather that dysbiosis (the concept of imbalance of the microbial biofilm previously discussed) could act by itself as the pathogenic ‘unit’ (16). If

periodontal disease was caused by one or a few specific pathogens, the preferred therapeutic strategy would be a targeted alteration of the plaque microbiota rather than total biofilm removal (17).

The microbiome participates in multiple physiological, metabolic and immunological functions and its alteration, both quantitative and qualitative, can have significant consequences for general health (18). But this relationship could be bi-directional, in which periodontitis shares a common inflammatory component with several systemic diseases such as diabetes, rheumatoid arthritis or lupus erythematosus, which are also related to atherosclerosis. These diseases have also shown to cause an altered inflammatory response that could lead to a shift the oral microbiome and reduce bacterial diversity, therefore increasing the predisposition to periodontitis (19).

The study of the oral microbiome has provided a deeper understanding of periodontal disease and the role that bacterial communities play in its pathogenesis. These studies have showed new pathways on the host - oral microbiome relationship (20). The integration of the microbiome and other -omic approaches will enhance our ability to understand periodontal disease, but also will help to understand the systemic role of oral microbiome in the pathogenesis of other diseases such as atherosclerosis. The oral microbiota could contribute to the worsening of metabolic parameters of patients and new therapeutic approaches to treat and prevent metabolic diseases targeting the oral microbiota could be an innovative medical strategy (21).

CONFLICT OF INTEREST

The authors report no conflicts of interest related to this editorial.

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