**Psoriatic arthritis and periodontal disease.**

**Is there a link between them and whether microbiome-oriented treatment could influence the course of arthritis in the future?**

**Abstract**

A wide range of environmental factors, including oral microbiomeare focus of growing interest because they may be involved in the pathogenesis and clinical course of systemic inflammatory diseases, including psoriatic arthritis (PsA). Oral microbiome bacteriaare responsible for so-called periodontal disease (PD) and are likelyto induceand maintain a chronic inflammation in individuals with genetic susceptibility.PsA and PD share the same pathophysiologic mechanism, ie. dysregulation of inflammatory response of the host. Therefore, the interesting issue is whether there is any possible relationship between PsA and PDwith regard to clinical course, prognosis and response to treatment in these two entities. Currently the evidence regarding a link between the oral microbiome and PsA presented in this article is scarce and need to be further investigated.

**Key words**: microbiome, periodontal disease, psoriatic arthritis

**Introduction**

Psoriatic arthritis (PsA) is a chronic inflammatory joint disease almost always associated with skin plaques and nail changes, which belongs to the family of diseases called spondyloarthritides (SpA).

Periodontal disease (PD) is a chronic periodontitis due to infection of various bacteria resulting in inflammation within supportive tissues of the teeth, progressive attachment loss and bone resorption and is characterized by formation of pockets and gingival recession (1).

A variety of environmental factors, including microbiome – intestinal and oral – are of growing interest since they might be involved in the etiology and pathophysiology of many inflammatory diseases, including PsA. These environmental factors are likely to take part in inducing an inflammatory disease especially in individuals with certain genetic susceptibility.

A link between PsA and inflammatory bowel disease (IBD) is well-established (2). The bowel microbiome might affect several extra-intestinal sites, including joints. There is some evidence that pathways seen in the skin-bowel-joint axis in PsA are induced or at least mediated by the gut microbiome. Interleukin-17 (IL-17) seems to have a crucial function in this axis. Further discoveries of the role of this interleukin and other mediators may pave novel therapeutic approaches for the treatment of PsA.

PsA and PD share the same pathophysiologic mechanism – dysregulation of inflammatory response of the host. Therefore, the interesting question is whether there is any possible relationship between PsA and PD that may influence clinical course, prognosis and response to treatment in those diseases. Currently the evidence regarding a link between the microbiome and PsA is very limited.

**Periodontal disease and oral microbiome**

The oral cavity harbors over 700 bacterial species forming so called oral microbiome. Although dental plaque represents a relatively small biomass, it is characterized by a highly dense microbial community which is almost as diverse as those found in the intestinal tract (3). Additionally, when periodontal inflammation is evident, the junctional epithelium has greater permeability, with resultant challenge to microbial tolerance and immunogenicity.

The primary cause of periodontitis is supposed to be bacterial infection and the interaction between bacteria and immunologic system of the host (4). Monocytes, the peripheral blood mononuclear cells, which are stimulated by T cells are responsible for production of inflammatory cytokines, including tumor necrosis factor-alfa (TNF), inteleukin-1 (IL-1) and interleukin-6 (IL-6), which further upregulate release of various mediators, including metalloproteinases (MMPs) which in turn cause destruction of soft tissue and bone in periodontal region (5).

Therefore, from the pathophysiologic point of view, PD is characterized by chronic inflammation of the gingival tissues of the teeth initiated by pathogenic bacteria in dental plaque extending to the periodontal ligament, which leads to progressive local remodeling – loss of connective tissue and alveolar bone (6). Loss of periodontal ligament with the formation of soft tissue pockets between the gingiva and the tooth root create an anaerobic environment that provoke an immune response of the host to the chronic presence of plaque bacteria.

Epidemiologic studies show that as many as 10% to 15% of the adult population have severe or advanced periodontitis (7). Some bacterial species, eg. *T. forsythensis*, *P. gingivalis* and *Prevotella* family are found to be important pathogens in PD and were exclusively detected in synovial fluid in PsA and rheumatoid arthritis (RA) patients, thus indicating the pro-inflammatory potential of these bacterial species on the joint synovium (8,9).

PD not only have local effects on the dentition and tooth-supporting tissues but also may impact a number of systemic conditions, and therefore there is currently a growing interest in studying PD impact on several diseases, including PsA, RA, atherosclerosis (with sequel including myocardial infarction and stoke), diabetes mellitus and neurodegenerative diseases, such as Alzheimer's disease and other autoimmune diseases, eg. Hashimoto's thyroiditis. The evidence for an association between systemic diseases and periodontitis is strongest with cardiovascular disease and diabetes (6).

**Psoriatic arthritis and oral microbiome**

A significant proportion of patients with psoriasis, ranged 5-30%, develop PsA, which is a chronic arthritis characterized by persistent and relapsing joint and adjacent soft tissues inflammation and bone remodeling. The prevalence of PsA is estimated to be up to 420/100 000 people (10).Although etiology of PsA is complex and not fully investigated, there is an evidence that genetic, immunologic and same environmental factors contribute to the pathogenesis of this disease. Disturbances in the immunologic system involved in pathogenesis of PsA, are in particular B and T cells infiltrates and neoangiogenesis in the joints synovium along with an over expression of inflammatory cytokines, including IL-1 and TNF (11,12). TNF is responsible for bone and cartilage degradation due to augmentation of MMPs production, with typical for PsA radiologic structural damage pattern expressed as bone resorption (ie. erosions) and new bone formation (ie. osteoproliferation and ankylosis).

In general, the term spondyloarthritides or spondyloarthritis (SpA) is used to describe a spectrum of diseases which share common clinical features – axial and peripheral arthritis and enthesitis – and a common genetic predisposition with high prevalence of HLA-B27 antigen. These diseases include PsA, ankylosing spondylitis (AS), reactive arthritis (ReA), arthritis associated with inflammatory bowel diseases (IBD) and undifferentiated SpA (uSpA).

Elevated frequency of PD were observed in all patients with SpA without significant statistical differences between each subtype. Flemming et al. (13), in a larger study, found a higher prevalence, but less severe periodontitis in SpA subtype withIBD.Although HLA-B27 antigen is highly prevalent in SpA patients, especially in AS, no significant association between this antigen and aggressive periodontitis was found. However, it was discovered that SpA patients with aggressive periodontitis show a positive association with HLA-A9 antigen and a negative correlation with HLA-A2 and HLA-B5 antigens, which are not involved in pathogenesis of SpA to the degree established for HLA-B27 antigen (14).

Despite gut microflora diversity and alterations in its composition seen in IBD, the similar studies concerning composition and diversity of bacterial organisms in the plaque remains non-conclusive.

**The relationship between psoriatic arthritis and periodontal disease**

There is a very limited data whether PD and PsA affect each other. In other words, whether there is a link between these diseases remains to be revealed.

Moen et al., discovered higher variety and concentrations of DNAs from oral bacteria in joint fluid than in blood of patients with PsA and RA (8), what indicate preferential trapping of bacterial DNA in joints fluid rather than in the serum. Their results suggest that inflammation in the synovium of joints in these inflammatory systemic diseases might be perpetuating due to the bacterial DNA presence. They also found that mean number of oral bacterial spaces was significantly higher both in sera and synovial fluid in PsA and RA compared to healthy controls. In conclusion these authors supposed that oral bacterial DNAs from gingival and dental tissue could be important elements in initiating and maintaining chronic inflammation in joints of PsA and RA patients, thus representing the link between PD and PsA.

To further test the linkage between PD and PsA Üstün et al, examined periodontal status of 51 patients with PsA and 50 controls in cross-sectional study (15). They assessed pocket depth, clinical attachment loss (CAL),plaque index and gingival index. In their study the level of CAL was significantly higher in PsA than in control group and therefore the severity of periodontitis as determined by CAL examination was found to be greater in PsA patients. CAL is well-accepted as a gold standard in evaluation of the severity of periodontitis and also is considered to be a good measure of past disease activity (16). However, they did not find the statistically significant difference in frequency of PD between PsA patients and healthy controls. Nevertheless, their results – for the first time, suggest that in PsA patients the severity of PD is greater and should be taken into account as potential systemic health problem influence arthritis. Moreover, this finding strongly suggest the possible relationship between these two entities. The potential limitation of the study was the fact, that patients with PsA were treated with different anti-inflammatory and disease-modifying antirheumatic drugs (DMARDs), including non-steroidal anti-inflammatory drugs (NSAIDs), sulfasalazine, methotrexate and TNF-inhibitors that may influence inflammation both within bacterial plaque and joints. The advantages of the study were not to include patients or controls with other than PsA systemic diseases and that the smoking status and body mass index (BMI) were similar between groups, therefore minimizing the bias related to comorbidities and environmental factors strongly impacting periodontitis (17).Although plaque index (PI) were similar in both groups, the significantly higher CAL levels in PsA patients may confirm an impaired host response in this patients, which might be a result of a certain susceptibility of PsA patients to PD progression.

The question whether systemic disease can co-induce, and not only exacerbate the periodontitis was addressed in a work of Golub and co-investigators (18).They proposed “two-hit” model for explaining the link between chronic inflammatory disease and PD. The first “hit” is considered to be periodontopathic subgingival biofilm and its microbial products, ie. endotoxins, thus reflecting local inflammation. The second “hit” involves systemic biomarkers and mediators of inflammation due to inflammatory disease, such as PsA, RA and others, that are present in circulation and impact on local periodontal environment. These include CRP, cytokines, prostaglandins and MMPs, leading to complex periodontal pathology since they not only exacerbate the PD but also contribute to its pathophysiology and clinical course.

**Summary**

On one hand, translocation of microbial products or migration and redistribution of host immune cells primed by microbes, ie. from periodontal region to joints, blood or soft tissues in PsA can represent pathogenic link between these two diseases. Therefore, at this context PD might impact on the pathophysiology and clinical course of PsA. On the other hand, inflammatory disease such as PsA, *via* a wide range of mediators, including inflammatory cytokines and MMPs can influence the clinical course od PD, thus is responsible for the impact from PsA onto PD. Taking together, in such setting the periodontal microbiome seems to be an attractive therapeutic target since it is susceptible to different interventions, eg. diet modification, implementation of probiotics and antibiotics and/or anti-inflammatory drugs (19). These and other potential intervention, for instance modification of oral epithelium permeability of microbiome into the systemic circulation need to be further investigated – what might give a chance for the complex treatment of PD and PsA in the future.

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