IMMUNOLOGICAL IMPLICATIONS OF SYSTEMIC RISK FACTORS FOR PERIODONTAL DISEASE

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Abstract

The periodontal apparatus is very well connected with the rest of the human body, by means of vascular, lymphatic and nervous structures. These connections make the periodontal structures easily accessible to different distant pathologic mechanisms, such as inflammatory reactions, that can influence the onset and evolution of periodontal diseases. In certain situations, these influences have a mutual nature, transforming the relationship of the periodontal pathology with the systemic conditions into a bi-directional one. Understanding the mechanisms that drive and promote these pathogenic connections is important for offering periodontal patients a comprehensive treatment and for including periodontal screening for certain systemic diseases' patients.

Keywords: *periodontal disease, systemic risk factors, Immunological implications*

Introduction

The proinflammatory reaction are the result of a complex interplay of bacterial inhabitants of subgingival biofilm and macrophages from the periodontal tissues [1-3]. The release of inflammatory mediators and bacterial factors from the periodontal tissues into the systemic circulation induces a systemic inflammatory burden which interferes with the function of insulin receptors and lead to peripheral insulin resistance [3-5].

Data regarding the deleterious effect of chronic periodontitis on glycemic control in T2DM is controversial. Outcomes of a recent meta-analysis and several studies revealed a significant improvement of glycemic control, quantified using HbA1c, after periodontal therapy [6-9]. In contrast, some studies did not indicate a significant HbA1c reduction after periodontal therapy, the periodontal therapy failure to control the periodontal infection and associated

inflammation being a potential explanation for the controversial reports [8].

The association between these two chronic disease, diabetes and periodontitis is considered to be bidirectional. The mechanism involved in this association show that hyperglycemia cause the formation of advanced glycation products, microvascular diabetic chronic complications with are related with changes in cytokines secretion profile [10]

The relationship between diabetes mellitus (DM) and periodontitis has been reported in numerous studies. About this relationship it can be said that diabetes is a risk factor for periodontitis and periodontitis may have a negative effect on glycemic control [11]. Also, periodontal disease is an important factor for increased risk of diabetic complications [12]. Although DM and periodontal disease are different medical entities, they have mutual influence by biochemical mechanisms, at the cellular and molecular levels.

The composition of gingival crevicular fluid (GCF) generally reflects the inflammatory condition of gingival and periodontal tissues, and for this reason it has been of great interest to periodontal researchers. The GCF analysis provides information specific to that periodontal site.[13-15]. It's known that the initial periodontal therapy changes GCF cytokine levels in patients with aggressive and moderate to severe forms of chronic periodontitis [16]. This has been demonstrated by using an enzyme-linked immunosorbent assay (ELISA), showing that IL-12 increased after initial therapy, in contrast with IL-1β, IL-6, IL-8, IL-10, IL-12 and TNF- α that have remained unchanged [16]. In decompensated diabetic patients with poor control of glycemic status the severity of periodontal disease in T2DM is growing. A study focused on the level of interleukins in saliva showed that the IL-17 level and probing pocket depth were not affected by glycemic status [17]

Basically, the function of inflammatory cells, such as neutrophils, macrophages and monocytes is altered in diabetic individuals, the severity of periodontitis being tightly correlated with the impairment of chemotaxis [18]. Patients with severe periodontitis exhibit a reduction in the chemotactic ability of neutrophils compared to those with mild periodontitis or non-diabetic individuals with severe or moderate periodontitis [19]. In addition to changes in phagocytic and chemotactic function, some studies on diabetic subjects and periodontal damage have revealed other changes in cells involved in mediating the immune-inflammatory response in this association, including intracellular destruction and adhesion ability. These defects in the body's immune system may predispose people with T1D to periodontal harm [20].

Other studies also display cytokine alterations in the salivary /gingival fluid, and / or gingival tissue in individuals suffering of diabetes and periodontal injury compared to healthy subjects [21,22], although independent studies performed on the same subjects category, could not obtain the same evidence [23].

Immunohistochemical studies have shown the predominance of Th17 and Treg cells in type two diabetic individuals affected by periodontal breakdown, compared to non-diabetic subjects with periodontitis [22]. The subsets of Th17 and Th1 cells involved in bone resorption regulation constitute important pool of cytokines such as IL-17 and RANKL (receptor activator of nuclear factor kappa-B ligand), which have elevated levels in individuals with diabetes and

periodontitis [24]. For these subjects,some studies describe a link between glycemic control and gingival fluid levels of cytokines such as IL-17 or those of the Th1 phenotype (IL-4).

To date, there is mounting evidence considering the adequacy of cytokine assay in early diagnosis in the subclinical stage of T2D and cytokine blockade by means of the therapeutic plan in T2D. Cytokine adjustments are also significant in the development of T1D, and their modulation is a possible remedy [25].

Regarding the means by which periodontal disease could have a contribution in the pathogenesis of cardiovascular disease there are several possible mechanisms:

1. Release of endotoxins in the blood stream;
2. The effects of heat shock proteins;
3. Altered lipid profiles caused by periodontopathogens which determine the oxidation and aggregation of low-density lipoprotein cholesterin;
4. Generation of acute-phase reactants such as CRP in the liver [26,27]

Most often, the initiation of CVD incidents is determined by the existence of atherosclerosis— accumulation of atheroma plaques in arteries due to endothelial damage which cause an immuno-inflammatory response. [28] Escalation of atherosclerosis can cause thromboembolisms which may ultimately cause an infarction and/or stroke [29].

This ongoing low grade subclinical inflammation, caused by acute and chronic inflammatory conditions diseases, hinders the function of endothelial tissue and the mechanical properties of blood vessels [30]. Concurrently, MMP-8 is secreted by smooth muscle cells that exist at the junction of the intima and media layer of arteries, thus promoting myogenesis. The hyperplasia of these cells induces fibrosis and the subsequent establishment of a fibrous plaque. In the course of time, cholesterol accumulates on the plaque and forms lipid streaks that can block the blood vessel. As lipid structures accumulate in excess this undermines the compact structure of the plaque and instigates its rupture causing thrombus formation. This in turn discharges thrombotic factors that promote coagulation when it comes in contact with platelets and can determine a thromboembolism [31,32].

Microbes frequently incriminated in the development of periodontal disease are more often than not gram-negative that promote increased bacteraemia after tooth brushing and routine dental procedures such as scaling, furthermore, periodontopathogens can penetrate endothelial cells and lead to malfunctions. [33]

As a result of this, periodontal microbes and their deleterious products are discharged into the systemic circulation via the ulcerated sulcular epithelium of the gingival tissue becoming a source of systemic inflammation through the release of inflammatory mediators, which can promote insulin resistance and possibly offer an explanation for the perio-systemic link [34-37].

Type 1 T-helper (Th1) responses are induced by the previously mentioned antibodies and inflammatory cytokines and help mobilize monocytes/macrophages to the affected site where the oxidized LDLs are engulfed, thus constituting foam cells and further generating atherogenesis. In

later stages foam cells go through a process of necrosis, releasing additional inflammatory stimuli, and through that creating the necrotic central area of advanced lesions [20].

Regarding the effect that periodontal treatment has on the evolution of cardiovascular diseases, recent literature reports moderate long-term beneficial outcomes on CRP levels – a marker for systemic inflammation and clinical criteria of endothelium function. CRP continues to be in a firm position as a relevant marker of CVD risk [38-40].

The pathophysiological mechanisms are explained by the participation of T and B cells, numerous soluble mediators (cytokines, effector cells), the existence of signalling pathways, which will cause irreversible joint damage to the synovial membrane, alveolar bone loss, which then covers most structures [41].

The clinical trials and meta-analyzes that have been performed, have demonstrated involvement in the host immune responses, of the balance between two categories of cytokines, resulting in increased serum concentrations in patients belonging to the group with joint damage compared to the group of healthy subjects. These results allowed the hypothesis to be issued, according to which destructive changes and inflammatory processes occurring in the joints are generated and maintained by both subpopulations of cytokines [42,43].

IL-13 is a soluble mediator released in close association with IL-4 by the Th2 lymphocyte subpopulation and plays an important role in the control of B lymphocyte activity, influencing the maturation, multiplication and differentiation into the antibody-producing cells. Thus, Zurawski G. observed high serum levels of IL-13 in patients with RA, concentrations that correlated with B lymphocyte proliferation [44]. Starting from this important role, this Th2 cytokine have been tested in animal models of arthritis, the results being considered promising in order to obtain new therapies [45].

Woods JM et al have revealed that considerable amounts of cytokines with strong pro-inflammatory activity such as TNF-α, IL-1β, IL-6 are secreted in the RA, but other less well-known cytokines are released (IL-18, IL-15, IL-33, IL-22). These results may conclude that in RA Th1 lymphocyte subpopulations are specifically involved and less type 2 Th, type 17 Th or regulatory Th cells. [46] Other researchers, such as Siloşi I et al, observed that the degenerative phenomena of the destructive phase are not controlled only by these cytokine imbalances but also by matrix production dysregulation processes, responsible for cartilage damage [47].

Leipe et al. [48] studied a specific subset of Th CD4+ lymphocytes with effector function, different Th1 and Th2 types, called Th17 cells, which secretes IL-17 as a pro-inflammatory cytokine. IL-17 is actively involved in inflammatory processes of many systemic conditions that have an autoimmune component. Regarding the involvement of IL-17 in RA, there are numerous mechanisms, such as stimulation of TNF-α and IL-1β, synthesis by macrophages, release of IL-6 and IL-8 in synovial fibroblasts, activated metalloproteinases, effects thereby modulating osteoclastogenesis and cartilage degradation. [49].

Other studies have found that IL-17 is involved in the inflammatory process both in the initial developmental stages of RA

and in the destructive phase of the disease, which is why there are ongoing studies to obtain biological therapy with monoclonal antibodies. [50,51].

Either involving periodontal tissues or developing into chronic liver diseases, the holistic and integrated setup of the human body allows common influencing and impact. The immune response tries to solve and repair certain pathological situations, but in this process, it can also aggravate and deteriorate the status of other developing conditions.[52,53] The periodontal and hepatic inflammatory reactions can have mutual influence and exacerbate one another, when existing in the same patient, by the synergetic action of the pro-inflammatory mediators. [54- 56]

The most common chronic medical diseases or conditions that are not spread by infection (non-communicable diseases-NCD) are cardiovascular diseases (CVD), diabetes mellitus (DM), pulmonary diseases, osteoporosis and chronic kidney diseases (CKD), all having common risk factors that contribute to about 40% of the total deaths [31,57].

CKD is a heterogeneous condition with the most serious adverse outcomes including debilitating metabolic complications of decreased GFR progressing to end stage renal disease (ESRD) and increased risk of cardiovascular disease (CVD). Epidemiologically, the most important risk factor for cardiovascular comorbidities of CKD is inflammation. The group of ESRD-patients with or without dialysis has high mortality rate, traditionally explained by the risk factors of atherosclerosis (diabetes, hypertension, dislipidemia). Lately there have been taken into consideration other factors contributing to the high rate of mortality such are inflammation, malnutrition and predisposition to infection [58-61].

Periodontal disease was recently highlighted as an important potential risk factor for NCDs. American Association of Periodontology defines chronic periodontitis, the most common periodontal disease, as an infectious disease that triggers periodontal inflammation leading to progressive attachment loss and bone loss and consequently periodontal pocket formation and/or gingival recessions [62]. Numerous recent studies support the contribution of periodontitis to chronic systemic disease such is diabetes mellitus and atherosclerosis, both recognized etiological factors for chronic kidney failure.

In 2017 in Romania the first comprehensive study which aimed to explore the link between periodontal disease and quality of life was developed, assessed with the Short Form 36-Item Health Survey in haemodialysis patients. [63] The study showed a high prevalence and severity of periodontal disease, evaluated with the gingival and periodontal index. High scores of the gingival and periodontal components of the index were associated with low QoL, both on physical and on mental components in this group of patients [64, 65].

CKD itself is a complex disease with numerous comorbidities all recognizing as a common link the inflammation. ESRD is treated either through dialysis or renal transplant. It is known that dialysis increases the inflammatory burden. The already challenged host, often associates periodontitis that increases even more the overall systemic inflammation. Cytokines seem to be the common link between pathophysiologic mechanisms of these diseases.

Acknowledgments
Alexandra Martu, Simona Popa and Mihail Virgil Boldeanu contributed equally with the first author.

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