THE BIOMOLECULAR AND BIOCELLULAR MECHANISMS INVOLVED IN THE PATHOLOGY OF THE ORAL CAVITY IN CASE OF SYSTEMIC DISEASES. REVIEW

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Abstract

The specialized literature exhibits a multitude of studies that highlight the role of general factors, of some chronic systemic diseases, that can contribute to the appearance or modulation of periodontal disease, carious disease but also of other oral diseases. The oral cavity can be affected by diabetes, which can lead to several complications, including tooth decay, periodontal disease, disorders of the oral mucosa and dysfunction of saliva, which have a significant effect on the quality of life of diabetic patients. The importance of the host lies in the association of systemic diseases to the process of periodontal destruction of tissues in the oral cavity (periodontal tissues, dental tissues, tissues of the oral mucosa and salivary glands).

The biomolecular and biocellular mechanisms involved in the pathology of the oral cavity in case of systemic diseases involve the mechanisms of local and systemic inflammation governed by proinflammatory cytokines (IL-6, IL-18, IL-17, IL-1B, IL-8, TNF- alpha and prostaglandins E2-PGE2, protein-2 inhibitory macrophages, MCP-1, interferon gamma, adipokines more common in diabetes. Inflammatory-mediated cytokines and proteins are practical markers of increased risk of cardiovascular disease, such as C-reactive protein (CRP), interleukin-6 (IL-6) and tumor necrosis factor - alpha (TNF-α), fibrinogen.

Keywords: *inflammatory mediators, cytokines, oral disease, periodontal disease, systemic disease*

Introduction

In the specialized literature we can find a multitude of studies that highlight the role of general factors, of some chronic systemic diseases, which can contribute to the appearance or modulation of periodontal disease, carious disease but also of other oral diseases. [1] Among these systemic diseases, the most common are analyzed: diabetes, cardiovascular diseases, kidney diseases, rheumatoid arthritis, autoimmune diseases, hematogenous diseases, oncological pathology, etc.).

Periodontal disease, that can begin with gingival involvement and can be complicated by chronic or aggressive periodontitis, is a complex condition that presents through the complex interactions host - pathogen the variability of the forms of clinical manifestation in relation to bacterial etiology; the host's immune response; clinical progression of the disease. The importance of the host lies in

the association of systemic diseases with the process of periodontal destruction.

I. Biomolecular and biocellular mechanisms in the context of systemic pathology - periodontal disease.

One of the most serious diseases of the oral cavity, periodontopathy, according to the latest studies, has a still high prevalence, especially the population over 65 years, keeping the highest chance of having the disease and developing severe forms. Periodontal disease is defined as any pathological change of periodontal tissues, [2] as a result of inflammation caused by the bacterial biofilm adjacent to the affected area.[3] Depending on the degree of disease, incipient forms, such as gingivitis, can be alleviated by strict hygiene of the oral cavity. Severe forms can lead to loss of connective tissue and maxillary alveolar bone tissue.

The causes of periodontopathy are multiple, but independent in determining the PR (probability ratio). [4, 5]

Ryden L. et al. [6] analyzed the data obtained from the PAROKRANK study, concluding that there is a statistically significant relationship between the presence of periodontopathy and the risk of first myocardial infarction. The mechanisms underlying this relationship have been analyzed in several studies, the amount of CRP [7] IL-6 [8, 9] the presence of Porphyromonas gingivalis [10,11] - the parameters suspected to be responsible for the systemic effects of periodontitis , especially the onset and maintenance of the inflammatory process, and IL-6 is recognized both as atherogenic interleukin but also with atheroprotective properties and contributes to the link between periodontopathy and atherosclerosis: The association between hypertension and periodontitis uses [12] the same mechanisms. [13]

1. Biomolecular and biocellular mechanisms in the context of heart disease (CHD) and periodontal disease

Destructive periodontal disease, involving Gram-negative bacteria, has been reported to be a significant predictor of coronary heart disease. [14] Because both heart disease (CHD) and periodontal disease have a multifactorial etiological character, as well as a wide variety of cofactors, a clear consensus on the importance of the relationship between these two conditions has been difficult to obtain. Mattila et al. were the first to show a statistical association between dental infections and coronary atherosclerosis. [15]

Several studies have examined the parameters of periodontal disease or other oral diseases in relation to intermediate variables or biomarkers of cardiovascular disease. One such example is the finding made by Kweider et al. (1993) that severe gingivitis was associated with an increase in leukocyte counts and serum fibrinogen levels [16] Wu et al [17] reported that elevated serum levels of CRP and fibrinogen, both well-established biological markers for cardiovascular disease, were also associated with periodontitis, while Mattila and colleagues [18] reported that dental infection was significantly associated with increased von Willebrand factor antigen.

Another important heart condition is acute myocardial infarction. There are many studies that have shown the relationship between periodontal disease and this serious condition. Thus, in a study conducted by Janket et al in 2003 [19], this association between periodontal disease and fatal heart disease was presented. The authors demonstrated that a number of potential mechanisms may play an important role in the association of the two conditions. Thus, they suggested that both the hypertrophic heart and the periodontium may have microcirculatory dysfunctions and arteriolar and capillary rarefaction. [20, 21] On the other hand, the authors observed that pressure overload

can induce left ventricular hypertrophy and general narrowing of the luminal diameter of the micro-vessels, resulting in vascular rarefaction. This can lead to ischemia in the heart and periodontal tissues.

A meta-analysis by Jukka HM and colleagues in 2003 [22] concluded that possible mechanisms by which oral infections could contribute to cardiovascular disease include a direct effect of microorganisms in the formation of endothelial atheroma, indirectly mediated by the response host or a genetic predisposition to pathogenesis.

2. *Biomolecular and biocellular mechanisms in the context of kidney disease and periodontal disease*

At the renal level, Han SS et al. noted the pro-hypertensive effect of Th1-type cytokines expressed as a result of stimulation with specific *P. gingivalis* antigen. [23] Thus, given the clinical association between periodontitis and chronic renal failure, [24] Borgnakke WS et al. highlighted the increased risk of death from cardiovascular disease in patients with periodontal disease associated with chronic renal failure. [25] Analytical models have been proposed, based on the relationship between ICR and periodontitis mediated by hypertension. [26] However, except for low levels of IL-18, a proinflammatory cytokine, there are insufficient data on the effect of periodontopathy treatment on the progression of kidney disease. [27]

3. *Biomolecular and biocellular mechanisms in the context of diabetic disease and periodontal disease*

Diabetes and periodontal disease are two chronic pathologies whose global prevalence has increased and which maintain complex clinical and biological relationships. The increase in the incidence and severity of periodontal disease in diabetics is evidenced by numerous epidemiological studies. The specifics of periodontal treatment in diabetics are related to immunosuppression which may delay healing, but its effectiveness is demonstrated, while the pathological mechanisms are far from being fully elucidated.

The very high level of glucose in the gingival fluid of diabetic patients could be a favorable environment for the development of a specific and pathological microbial flora. However, numerous clinical studies performed on the composition of the subgingival plaque of diabetic and non-diabetic patients have failed to highlight the impact of diabetes on the periodontal microbiota. There are also links between the level of glycemic control (HbA1c) in diabetics and the composition of the subgingival plaque. [28]

Numerous studies are of interest in diabetic PMN dysfunction in connection with the prevalence and severity of periodontal disease. Some animal clinical studies appear to indicate that adhesion, chemotactism (decreased IL-8), and phagocytosis of both peripheral and gingival neutrophils are impaired in patients with type 2 diabetes. [29]

Studies by Salvi and colleagues in 1997 showed that monocytes in patients with type 1 diabetes produce more cytokines and proinflammatory mediators such as interleukin IL-1B, TNF-alpha and prostaglandins E2 PGE2 in response to bacterial aggression (especially lipopolysaccharides or LPS) compared to persons without diabetes. [30]

Recently, a third cell type has been implicated in the pathology of periodontal disease in diabetics: T lymphocyte. In fact, T lymphocytes played a role in the dysfunction of macrophage inflammatory infiltrate observed in adipose tissue in patients with or without diabetes. Different subpopulations of T lymphocytes exist and often follow the environment of pro or anti-inflammatory cytokines. It appears that patients with unbalanced diabetes or

periodontal disease have more Th 17 lymphocytes (secreted interleukin 17, proinflammatory) and T lymphocytes compared to patients with periodontitis, but not diabetic. The involvement of cytokines, adipokines and proinflammatory mediators is important in the pathology of periodontal disease in the diabetic patient. [31]

Other mediators of inflammation could participate in the pathology of periodontitis in type 2 diabetics such as interferon gamma, protein-2 inhibitory macrophages, MCP-1 or TNF alpha. Proinflammatory cytokines are not the only molecular mechanisms involved in the pathology of periodontal disease in subjects with diabetes. Finally, adipokines (cytokines produced by adipose tissue), leptins, resistin, adiponectin could be involved in the relationship between diabetes and periodontal disease. [32]

4. *Biomolecular and biocellular mechanisms in the context of rheumatoid arthritis and periodontal disease*

Rheumatoid arthritis is a systemic inflammatory disease with unknown etiology and an autoimmune pathology, characterized by distorting and destructive arthropathy with development of musculoskeletal system, but also with multiple systemic manifestations. Latest research showed a similarity between periodontal disease and rheumatoid arthritis because of autoimmunity elements that characterize both diseases. As the periodontal disease as well as in rheumatoid arthritis, in terms of the immune response, there are common elements by increasing the number of cytokines, T lymphocytes and lipid mediators. [33]

In this context, they have investigated several biomarkers, including interleukin (IL-1β), protein C-reactive, metalloproteinase matrix (MMP 8 and MMP 9), tissue inhibitor of matrix 1 of metalloproteinase, tumor necrosis factor (TNF-α), receptor activator of nuclear factor-k B and pyridinoline reticulate carboxyterminal type I of collagen telopeptide. Periodontal disease has several clinical and pathogenic characteristics common with rheumatic disease.

Periodontal diseases are not only a risk factor for tooth- periodontium complex, but can also be a threat to general health. [34]

Cytokines regulate the intensity and duration of immune response by stimulating or inhibiting the activation, proliferation and / or differentiation of different cells by regulating the secretion of other cytokines or antibodies or, in some cases, by effectively inducing the death of the programmed cells in the target cell. In addition, cytokines can modulate the expression of different cell surface receptors for chemokines, other cytokines or for themselves. [34]

A cytokine that induces differentiated biological effects depending on the nature of the target cells is considered to have pleiotropic action. Cascade induction occurs when the action of a cytokine on a target cell induces that cell to produce one or more additional cytokines. [35]

The initial response to bacterial infection is a local inflammatory reaction that activates the innate immune system. Amplification of this initially localized response results in the release of a series of cytokines and other mediators and the spread of inflammation through the gingival tissues. [36] Failure to encapsulate this "inflammatory assault" in gingival tissue leads to the expansion of the response adjacent to the alveolar bone. The inflammatory process then leads to the destruction of connective tissue and alveolar bone, which is the cardinal sign of periodontal disease (PD). [37]

Secondly, inflammatory mediators must penetrate the gingival tissue to reach a critical distance from the alveolar bone. [38] Achieving critical concentrations of inflammatory mediators leading to bone

resorption depends on the expression of proinflammatory cytokines such as, but not limited to interleukin (IL) -1, -6, -11 and -17, tumor necrosis factor alpha (TNF- α), leukemic inhibitory factor and M oncostatin. [39, 40]
Particularly, IL-17 enhances the production of various proinflammatory molecules including TNFα, prostaglandin E2 (PGE2), IL-6 and IL-1β, facilitating bone resorption via osteoclast activation.

II. Biomolecular and biocellular mechanisms in the context of diabetes - carious disease.

There is also an important link between carious disease, namely, the increased cariogenic risk that the patient suffering from cardiovascular disease may have. Inflammatory-mediated cytokines and proteins are practical markers of increased risk of cardiovascular disease, such as C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α). [28 , 40] Bacterial species located at the level of root caries induce systemic inflammation and immune response, thus increasing serum levels of CRP and serum IgG. [41]

The oral cavity can be affected by diabetes, which can lead to several complications, including tooth decay, periodontal disease, disorders of the oral mucosa and dysfunction of saliva, which have a significant effect on the quality of life of diabetic patients. [42] Untreated oral conditions may also increase the risk of poor metabolic control.

Maintains the integrity of oral tissues, provides protection against bacterial, fungal and viral infections and controls the balance between demineralization and remineralization of teeth.

Increased glucose levels in saliva affect the activity of microorganisms. *Streptococcus mutans* and *Lactobacillus* are considered to be the most cariogenic bacteria because they have the ability to create an environment with low pH and the progression of caries. [43]

Unbalanced diabetes is associated with significant cariogenic changes in the oral environment, such as: resting and stimulated salivary flow is lower, lower saliva buffer capacity and acidic pH, higher salivary glucose, higher concentrations of salivary albumin, high proportion of *Streptococcus mutans*. [44]

Reduced salivary flow caused by hyperglycemia is characteristic especially in periods with poor metabolic control of diabetes. During this period, the presence of glucose in the oral cavity may occur, thus facilitating the development of acidic and acidogenic bacteria and the development of carious lesions. The main complications of diabetes affect organs and tissues rich in capillaries, such as the kidneys, retina and nerves. These complications are secondary to the development of microangiopathy. Similar changes in small vessels can be found in the oral tissues.

Xerostomy is a subjective manifestation of dry mouth, while hyposalivation is an objective decrease in salivary flow. The oral cavity can be dramatically affected by diabetes. These oral complications have important effects on the quality of life of patients with diabetes and can also directly and indirectly affect glycemic control. Oral lesions and conditions associated with diabetes include xerostomia, burning sensation, gingivitis, periodontal disease, tooth decay, and oral candidiasis.

Elevated salivary glucose levels, decreased salivary flow, and low salivary pH are well known risk factors for dental caries. These quantitative changes in salivary secretion and qualitative changes in salivary blood glucose were closely correlated with type I diabetes. The high value of salivary glucose was also correlated with hyperglycemia. [45] Unsatisfactory oral hygiene and not following a recommended diet are

considered factors associated with increased cariogenic risk. [46]

Several studies have reported a high prevalence of xerostomia and hyposalivation in diabetic patients.

A very high and severe prevalence of dental caries is found in diabetic patients compared to non-diabetics. It has been reported in the literature from previous studies that the risk of carious lesions is more common in patients with type II DM compared to non-diabetics. [47]

In saliva, there are three major systems that contribute to the buffer capacity: bicarbonate, phosphate and protein buffer systems. The buffering capacity of saliva is an important factor, which plays an important role in maintaining salivary pH and dental remineralization.

Conclusions;

The biomolecular and biocellular mechanisms involved in the pathology of the oral cavity in the case of systemic diseases involve the mechanisms of local and systemic inflammation governed by proinflammatory cytokines and other mediators of chronic inflammation.

The importance of the host lies in the association of systemic diseases to the process of destruction of tissues in the oral cavity (periodontal tissues, dental tissues, tissues of the oral mucosa and salivary glands)

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