Periodontal disease and systemic health

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ABSTRACT

Periodontitis is a chronic inflammatory disease of the oral cavity that usually affects the adult population. In the last two decades, many specialized studies have reported that there is a link between periodontitis, cardiovascular diseases and diabetes mellitus. Main factors that lead to periodontal disease installation are several bacterial species that induce both local and systemic inflammation, negatively contributing to the progression of cardiovascular diseases. One of the many complications of diabetes mellitus is periodontitis, there is a two-way relationship between these two diseases. The purpose of this review is to analyze the recent data provided by the literature regarding the relationship between oral periodontal pathogens and systemic health.

Keywords: bacterial pathogens, inflammation, diabetes mellitus, cardiovascular diseases

PERIODONTAL DISEASE PATHOGENESIS

Periodontal diseases are divided into two groups: reversible and irreversible. Gingivitis is a reversible inflammatory condition due to dental plaque accumulation, affecting approximately 50% of the adult population. It is characterized by an initial increase in blood flow, increased vascular permeability and an influx of cells (polymorphonucleated leukocytes (PMNs) and macrophages) from the peripheral blood to the periodontal connective tissue (1-3).

Periodontal disease is the most common chronic inflammation of the oral cavity in the adult population worldwide. 35% of the adult population world wide has periodontitis, 11% have a moderate or severe form, this oral disease beeing considered a pandemic health problem that causes disabilities, speech impairment, low self-esteemand reduced quality of life (4,5).

This chronic inflammatory disease affects the supporting tissues of the tooth, leading to the progressive destruction of connective tissue and alveolar bone (5,6). After initiation, the disease progresses with the loss of collagen fibers and their disintegration from the cement surface, apical migration of epithelial cells, formation of periodontal pochets and resorption of alveolar bone. If left untreated, the disease continues with the progressive destruction of the bone, leading to tooth mobility and finally tooth loss (5-7).

The role of microorganisms in the etiology of periodontitis has been very well studied, so between 500-700 bacteria species are able to colonize oral cavity. 10% of these bacteria plays important roles in the initiation of periodontal disease. Periodontitis is initiated by colonization of the gums by pathogenic bacteria such as *Porphyromonas gingivalis, Actinobacillus actinomycetemcomitans* and *Bacteriodes forsytbbus. P. gingivalis, Tanerella forsythensi* and *Troponema denticola*, are directly associated with chronic periodontitis. *A. actinomycetemcomitans* has been observed in thee early

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stages of periodontal disease and in aggressive periodontitis (8,9).

These bacterial species have the ability to activate local defense mechanisms, destroy the epithelium and other structures of the gingiva, while inactivating ther repairs systems. Activated neutrophils present at the site of inflammation are immobilized and produce reactive oxygen species (SRO) that are capable of destroying the pathogens. ROS overproduction can damage the surrounding host tissue (8-10).

There are a number of systemic factors that can contribute to the progression of periodontal diseases such as heredity, nervous system disorders (psychicstress), endocrine imbalances (diabetes), immune deficiencies, cardiovascular, hematological, hepatic, renal diseases and nutrition deficient (2,11).

Are three important biological stages in the progression of periodontal disease: inflammation, connective tissue degradation and the last one bone turnover. Inflammation in periodontal disease is response to bacterial plaque acumulation, permanent presence of bacterial multispecies, leads to chronic inflammation and abundance of oral inflammatory biomarkers (6,8,9). Many studies have detected various inflammation biomarkers to be increased both saliva or gingival crevicular fluid (GCF) in patients with periodontitis. Interleukin-1 (IL-1), IL-6, C-reactive protein (CRP) tumor necrosis factor-alpha (TNF-α), prostaglandin E2 are specific biomarkers to the inflammatory process which have been detected both in total unstimulated saliva and also CGF, where they present increased levels (6,9, 12-17). Reactive oxygen species (ROS) can be generated by inflammatory reactions, especially chronic ones. Inflammatory cells such as activated neutrophils and macrophages release different types of ROS such as $O_2^{\cdot-}$ $O_2^{\cdot-}$, H_2O_2, $HO^{\cdot}$ and $HOCl$ (18). The production of ROS by the PMN under inflammatory conditions ensures a protective role for the host. Overproduction of ROS by PMNs, leads to oxidative damage of gingival tissue, periodontal ligament and alveolar bone (19-21).

8-hydroxydeoxyguanine (8-HOdG-biomarker of DNA damage), malondialdehyde (MDA -marker of lipidperoxidation) were detected to be increased in saliva and serum of patients with chronic periodontitis. At the same time, statistically lower levels of uric acid, catalase and glutathione peroxidase were detected in saliva and serum of patients with chronic *versus* healthy volunteers (20-23).

Matrixmetalloproteases (MMPs) are local proteinases responsible for both degradation and remodeling. During periodontal disease evoluation, collagen fibers are destroyed by interstitial collagenases, derived from the host cells. A collagenase capable of degrading the structure of the triple helix of type I, II, III collagen in the alveolar bone matrix is collagenase 2 or MMP-8. MMP-8 is released in increased levels when the PMNs are mobilized to inflammation site (23,24). Increased salivary or GCF levels of MMP-8, myeloperoxidase (MPO) and tissue inhibitor of matrix metalloproteinases (TIMP)-1 were detected in patients with periodontal disease. Osteocalcin is a specific marker of bone, his release may induce a new osteoid synthesis or resorption of the alveolar bone. Increased salivary statistically levels of osteocalcin was observed in patients with periodontal disease (23,25). Type I collagen C-terminal telopeptide (CTX) is one of the most studied members of collagen degradation molecules, which present an increased salivary level in patients with chronic periodontitis (23). An organism's response to periodontal infection involves the release of enzymes from stromal, epithelial, inflammatory or bacterial cells. Detection of these enzymes in saliva and GCF may help to clarify the pathogenesis of periodontal disease. Important roles in tissue degradation are played by enzyme ssuch as: elastases, gelatinises and proteinases. Aspartate aminotransferase (AST), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), acid phosphatase (ACP), glutamyl transferase (GGT) and creatine kinase (CK) are intracellular enzymes that are released in a large amount from the injured cells of periodontal tissues in FCG and saliva as well as in surrounding fluid. These enzymes usually present increased levels in patients diagnosed with periodontal disease (26,27).

PERIODONTAL DISEASE AND DIABETES MELLITUS

Between diabetes and periodontal disease has been observed a bidirectional relationship, in which diabetes increases the risk of developing periodontal disease and periodontal inflammation negatively affects glycemic control. Diabetes mellitus is a chronic metabolic disorder that affects the population worldwide, which can be characterized either by the lack of insulin production by the pancreatic beta cells (type 1 diabetes), or by insulin resistance (type 2 diabetes), conditions that will leads to hyperglycemia (28,29).

Diabetes mellitus has a number of well-known complications such as retinopathy, nephropathy, poor wound healing, neuropathy, macro and micro-vascular impairment and periodontal disease (29,30). An observational study conducted by De Miguel-Infants and coworkers in adults aged 40 or older, observed that diabetic patients have an increased risk of developing periodontal disease (31).

Chronic inflammation that is specific during the periodontal progression causes an exacerbated inflammatory response correlated with low metabolic control of serum glucose and increased insulin requirements (32). In patients with type 2 diabetes mellitus, Aikten JP and coworkers detected a positive correlation between salivary levels of alpha-2-macroglobulin and HbA1C, this aspect reflecting that the glycemic control of patients can also be performed at the salivary level (33). The salivary concentration of melatonin has been detected to be decreased in patients with type 2 diabetes mellitus and in patients with periodontal disease, which may be a key biomarker in the diagnosis and treatment of the two diseases (34). Patients with gingivitis or periodontitis, diabetic patients, present increased levels of glucose, α- hydroxybutyrate and biomarkers of oxidative stress (35). In a study conducted by Liu and coworkers on diabetic mice it was observed that periodontal disease aggravated pancreatic β-cell failure and induces insulin resistance (36). Individuals with acute bacterial or viral infection are unfortunately characterized by severe and long-lasting insulin resistance. This aspect being confirmed by Fernandez -Real JM and coworkers in a study of 124 infected middle-aged men with enteroviruses and *C. pneumonia* (37).

Sugiyama S et al. observed in a diabetic rats study infected with *P. gingivalis* a decrease in gingival vascular function and increase in insulin resistance (38). Diabetic patients have a 3-fold higher risk of developing periodontitis compared to healthy individuals (39).

An incidence of periodontal disease of 58% was observed in patients with type 1 diabetes, compared with non-diabetic patients, who had a 15% incidence (40). Diabetes mellitus causes morphological changes in the salivary glands and in saliva composition, so Malicka B and cowerkers observed in diabetic patients that myeloperoxidase and salivary Ig A were correlated with poor periodontal status (41). Increased serum levels of inflammation mediators such as CRP, TNF-α, and IL-6 were detected in both patients with periodontal disease and diabetic patients (42-44). OS is a major link be-

tween the 2 diseases, plasma and salivary levels of OS have been detected to be increased in both conditions that further can activate pro-inflammatory systemic pathways (45).

PERIODONTITIS AND CARDIOVASCULAR DISEASES

Cardiovascular diseases is a major cause of death worldwide including in Romania. Diabetes, smoking and inflammation are risk factors for both myocardial infarction and periodontal disease (46-50). Have been observed a possible association between cardiovascular diseases and periodontitis, but the role of oral infection at the cardiovascular level is not fully elucidated. The results of cohort studies observed that people with spinal cord disease have a 2.22-fold higher risk of developing cardiovascular diseases (51). Pussinen PJ and coworkers detected at 1163 men patients with coronary heart disease in serum antibodies against *P. gingivalis*, and *A. actinomycetemcomitans* (52).

Figuero E and coworkers detected in 42 atheromatous plaques, bacteria specific to periodontal pathology such as *P. gingivalis*, *A. actinomycetemcomitans*, *T. forsythia*, but also other bacterial types such as *Eikenella corrodens, Fusobacterium nucleatum and Campylobacter rectus* (53). The results of this study confirm that oral periodontal pathogens may migrate to other body sites. Studies in mice receiving a hyperlipidic diet to develop atheromatous plaque and infected with *P. gingivalis* and *T. denticola* have shown that the presence of these bacteria is associated with alveolar bone loss and aortic atherosclerosis (54).

P. gingivalis and *T. denticola* can induce a systemic immune response, their bacterial genomic DNA being detected in the oral epithelia and aorta. *P. gingivalis* being the only oral bacterial species that induces the expression of virulent factors associated with platelet aggregation (55). Salivary amylase may be an independent diagnostic factor for acute myocardial infarction in patients suffering from precordial pain less than 4 hours.

The use of nano-biochips as a screening method based on salivary proteins such as CRP, myoglobin and myeloperoxidase may be beneficial for patients suffering from acute myocardial infarction (56,57).

Several studies have suggested a possible connection between periodontal disease and endothelial dysfunction, caused by reduced bioavailability of nitric oxide, that reduces platelet aggregation, inhibits leukocyte attachment to endothelial cells,

and prevents the expression of adhesion molecules (58,59). Studies on rats with periodontitis confirmed the reduction of nitric oxide level and the correlation with endothelial dysfunction (59-61).

Endotoxins and antigens secreted by periodontal pathogens contribute to the pathogenesis of endothelial dysfunction, by stimulating the attachment of leukocytes to the surface of entothelial cells, may induce the expression of adhesion molecules such as endothelial monocytes chemoattractantprotein -1 (MCP-1), may induce a significant rise and release of entothelin-1 (62,63). Has been observed that periodontal treatment supplemented with antibiotics improve endothelial dysfunction (64). Stroke presents a number of well-known risk factors such as hypertension, dyslipidemia, diabetes, smoking and age. Numerous epidemiological studies have also included periodontal disease as a major risk factor (65,66). Increased serum levels of CRP and antibodies against *P. gingivalis* have been associated with acute ischemic stroke (66,67). Per-

iodontal pathogens can be found in heart valve tissue, atrial and ventricular tissues, can colonize atheromatous plaque (68,69).

In conclusion, periodontal pathogens or their endotoxins induce an inflammatory response both locally and systemically. *P. gingivalis* is the most aggressive pariodontal pathogen at cardiac level being able to induce platelet aggregation and the expression of numerous adhesion molecules contributing in this way to the progression of cardiovascular diseases. Children and adults who have been diagnosed with type 1 and type 2 diabetes have a rather high risk of developing periodontal disease. Periodontal disease should not be ignored and proper treatment will greatly improve the patients health both locally and systemic.

Acknowledgement

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