Advances in the Relationship between Periodontitis and Systemic Diseases

Summary

New investigations have definitely acknowledged a clinically relevant two-way relationship between periodontitis and certain systemic diseases and conditions which are significant for the dentist in daily practice, and for a physician as well. This review article yields the most up-to-date information on the role of periodontal disease in systemic diseases that include cardiovascular diseases and atherosclerosis, diabetes mellitus respiratory diseases and unfavorable pregnancy outcomes. It debates the role of diabetes and smoking in the periodontal tissues.

Key words: periodontitis, systemic diseases, systemic conditions.

Introduction

Periodontitis is considered to be the most frequent oral disease. Microorganisms - bacteria, its parts and products of their metabolism are responsible for its development, and for the destruction of the supportive apparatus of the tooth. From the large number of the bacteria dwelling in the biofilm on the tooth surface, Porphyromonas and Prevotella (previously black pigmented Bacteroides species), Bacteroides forsythus and Actinobacillus actinomycetemcomitans have been emphasised because of their pathogenic influence on the periodontal tissue. The microorganisms of the dental plaque, and their metabolic product may - especially in advanced cases of the disease - enter the blood stream during mastication or therapeutical procedures. The consequences may occur in the most distant organs, which is the case in the development of subacute endocarditis, some respiratory diseases (pneumonia, emphysema, chronic obstructive pulmonary disease), coronary heart disease, atherosclerosis and ischaemic stroke, and diabetic glycemic control changes.

In the light of the of these investigations, it seems that "focal infection" from the beginning of the twentieth century is gaining ground in its new apparition. Furthermore, the influence of some systemic factors on the periodontium is well studied and such systemic factors are today considered risk factors.

Systemic risk factors of periodontal disease are divided in two groups (1). The first group consists of smoking and diabetes mellitus. The influence of these two conditions on the development and progression of periodontal disease is based upon cross-sectional, longitudinal and intervention studies and mechanism studies. It is reasonable to call them real risk factors, which must be taken into account in the treatment of periodontal disease. The second group of factors associated with periodontal disease is related to an earlier stage of development and understanding and are probably best called risk factors.
indicators: osteopenia and osteoporosis; stress, distress, and coping; dietary factors (calcium and vitamin C), medications and genetic factors. In this group there are also some immune system diseases such as AIDS; primary and secondary neutrophil disorders (congenital neutopenia and drug-related agranulocytosis; and diseases affecting host response (Sy Papillon-Lefevre, Sy Ehlers-Danlos, hypophosphatasia), although these diseases are associated with more severe diseases in juveniles and probably significantly increase the risk of periodontal disease.

There is increasing evidence that a number of complex diseases is related to opportunistic infections that have their source in periodontal disease. Subsequently, there has been increased interest in oral microbiology, oral mucous immunity and connection to systemic diseases such as pre-term low birth weight, pulmonary diseases, cardiovascular and cerebrovascular diseases. This review article gives insight into systemic conditions and diseases that might influence periodontal disease, but also those that might, in the course of worsening, be influenced by periodontitis.

Cardiovascular diseases and periodontitis

The relationship between oral infections and cardiovascular diseases in well known, particularly with respect to bacteriemias of oral source as a cause of bacterial endocarditis that may cause damage to heart valves. Here, we shall describe the most recent evidence of a correlation between periodontal disease and atherosclerosis, coronary heart disease (CHD) and stroke.

Atherosclerosis

Cardiovascular disease, which is usually atherosclerosis, is still the most frequent cause of death in Europe, the United States and part of Asia (2). Atherosclerosis is today considered to be an inflammatory disease. According to Ross response-to-injury hypothesis of atherosclerosis, the initial lesion is a result of an endothelial injury which causes chronic inflammation in the artery and, subsequently, atherosclerotic response (3).

One of the possible mechanisms is injury caused by infectious agents, provoking an inflammatory response, the like of which can be seen in atherosclerosis. The role of infection has been critically reviewed by Danesh et al (4). They have collected an ever-increasing databank of evidence which proves that Chlamydia pneumoniae, Helicobacter pylori, periodontal bacteria and cytomegalovirus infections can be related to cardiovascular diseases.

Coronary heart disease

A number of studies connect oral diseases and coronary heart disease. While earlier studies dealt with the oral cavity as a whole, recently emphasis has been on periodontal disease. De Stefano et al. (5) discovered that patients with periodontitis had a 25% greater risk of CHD, while the relative risk for males younger than 50 was 1.72. The results were adjusted for age and blood pressure, and partially adjusted for smoking.

Joshipura et al. (6) followed up more than 44,000 health workers for longer than six years. The subjects with periodontal disease and less than 10 teeth at baseline had the initial risk of CHD of 1.67.

Genco et al. (7) proved that baseline periodontal disease, for subjects younger than 60, was a predictor for subsequent CHD with relative risk of 2.68.

Published data suggests an increase in relationship between cardiovascular diseases (CVD) and periodontitis, especially in men younger than 60 - 65.

Ischemic stroke

Research carried out by Wu et al. (8) was based on a ten-year follow up of more than 10,000 subjects. Their results speak in favor of a connection between periodontitis and non-hemorrhagic stroke with a relative risk of 2.11. Further studies confirm the data on higher risk for non-hemorrhagic stroke in Caucasian and African men and women (9-11).

The relationship between oral diseases caused by microorganisms, especially periodontal disease, and CVD and nonhemorrhagic stroke, most of which is ischemic stroke, clearly points to a correlation between periodontitis and atherosclerosis and its sequelae, such as coronary heart disease and cerebral vascular disease.

Periodontitis and respiratory diseases

As early as 1968 Potter et al. described the presence of dental diseases in subjects with pulmonary
diseases (12). Oral bacteria can enter the lower respiratory tract by aspiration and cause pneumonia. Severe infections of the lungs can develop after aspiration of salivary secretion, especially in patients with periodontitis (13-16). 30 to 40% of aspiration pneumonia, predominantly necrotizing pneumonia or lung abscesses, has anaerobes in etiology, the most frequent organisms being *Proteus gingivalis* (PG), *Bacteroides oralis*, *Eikenella corrodens*, *Fusobacterium nucleatrum*, *Actinobacillus actinomycetemcomitans* (AA), *Peptostreptococcus* and *Clostridium* (17-26). It is possible that even *Streptococcus viridans* plays a role in the development and/or progression of pneumonia (22,29-32).

Bacteria may have an influence in exacerbations of chronic obstructive pulmonary disease (COPD) (33,34), where the dental plaque may serve as a reservoir of respiratory pathogens.

There is a number of possible mechanisms in the influence of bacteria on the pathogenesis of respiratory diseases:

- Aspiration of oral pathogens (PG or AA, for example).
- Alteration of the mucous surface by salivary enzymes in periodontitis, leading to an increase in adhesion and colonization of respiratory pathogens (35-44).
- Periodontal disease-associated enzymes may destroy salivary pellicles on pathogenic bacteria (45).
- Alteration of respiratory epithelium by cytokines from periodontal disease facilitating the infection of the epithelium with respiratory pathogens (46-53).

**Smoking and periodontitis**

The effect of smoking on periodontal disease has been studied in detail in a number of reports. Smoking has immunosuppressive effects that impair host defences by decreasing motility, chemotaxy and fagocytosis of polymorphonuclear leukocytes (PMN-L) in peripheral blood. Therefore, the first line of defence against subgingivally colonized bacteria is endangered (54-57). Smokers have a decrease in antibody production, especially IgG3 (58), the most responsible for colonization of periodontal bacteria, additionally to the smaller percentage of immunoregulatory T-lymphocytes (59).

Periodontal pathogens evade the specific and non-specific immune defence and colonize subgingivally. Smoking increases the adhesion of microorganisms on epithelial cells (60). It has been proven that smokers are more easily infected by *Bacteroides forsythus* and *Porphyromonas gingivalis* than non-smokers (61).

Nicotine has been found on tooth root surfaces of smokers (62). Cotinine, the main metabolic product of nicotine, can be found in serum, saliva and sulcus fluid of smokers (63). Exposition of fibroblasts to nicotine leads to a weakening of their proliferation (64), migration and adhesion to the root surface (65). They bind and fagocyte nicotine nonspecifically, which can lead to the metabolism, collagen synthesis and protein secretion alterations.

Smoking causes a chain of unfavorable reactions that include a weakened immune response, subgingival colonization of bacteria and toxicity of connective tissue cells. Altogether, it leads to an increase of periodontal disease expression and a weakened response of periodontal tissue during therapy.

**Diabetes mellitus and periodontitis**

The influence of diabetes mellitus (DM) on periodontal tissue is well known. It is difficult to come to widely accepted conclusions, since studies performed were not adjusted. Some studies on small samples suggest that there is an irrelevant influence of DM on periodontal tissue, while modern epidemiologic surveys clearly indicate that DM is a risk factor in periodontal disease, using modern epidemiologic methods. DM is often related to increased gingival inflammation as a response to plaque accumulation (66-68).

It is well known that young diabetic patients with poor glycemic control more easily develop periodontitis than older ones. Papanou reported on more severe cases of periodontitis in adult diabetics compared to the DM-free adults (69). A longitudinal study on Pima Indians showed that type 2 of DM (non-insuline dependent DM) is a significant factor for periodontal disease (70,71). DM not only has influence on the prevalence and severity of periodontitis, but it also plays a role in the progression of the disease (72).
It should be pointed out that a careful periodontal examination and detailed periodontal status assessment is an absolute necessity in patients with DM and periodontitis, in order to obtain a confident estimation of the response to periodontal therapy, since the presence of DM does not necessarily mean a worse prognosis and outcome of the periodontal disease.

**The mechanisms of influence of diabetes on periodontal tissue**

Possible mechanisms of the influence of DM on periodontal tissue consist of glucose level changes, subgingival flora components, blood perfusion, host response and metabolism of periodontal tissue (72). However periodontally affected sites in diabetics contain the same bacteria species as infected sites in patients without DM (73-75). Similar constitution of the subgingival flora might indicate that the cause for increased prevalence of periodontitis and more severe periodontal destruction in diabetics lies in the host response.

Increased levels of glucose in sulcular fluid in DM may adversely influence healing processes and local response to microorganisms (76).

Renal, retinal and neural vascularisation changes are also present in DM patients. Thickening of capillary endothelium lessens oxygen diffusion and thus changes the homeostasis of the periodontal tissue (77).

Advanced glycosilation endproducts (AGEs) production, according to Schmidt et al. (78), shows a two fold increase in the gingiva of patients with DM compared to patients without DM. The mechanism responsible for significant injuries of the vascular system might be the increased oxidation stress. Formation of AGEs stimulates the proliferation of smooth arterial muscles, thickening the walls of the blood vessel. Enhanced cross-linking of AGE-containing collagen in the basement membrane inhibits the normal degradation of these proteins, increasing the thickness of the membrane. In arteries, AGE-containing collagen binds the low density lipoproteins (LDL) that create atheromas and further narrow the vessel lumen. All these mechanisms can alter the response to bacterial invasion, and to the progression of periodontal disease (79).

In some DM patients a disturbance occurs in adherence, chemotaxy and phagocytosis of polymorphonuclear leukocytes (PMN-L) (72,80,81), although these disturbances were improved after glycemic control had been established. Oliver et al. (82) suspect that increased levels of β-glucuronidase point to hyperreactivity or an increase in the number of PMN-L in the gingival sulcus of uncontrolled diabetics.

It has been hypothesised that a great number of diabetic patients have a hyperreactive types of monocytes and macrophages, whose stimulation by bacterial antigens leads to a significant increase in cytokine production. (83,84).

Collagen metabolism changes lead to alterations in wound healing, initial periodontal lesion and progression of periodontitis. Matrix metalloproteinases (MMP) of periodontal tissue responsible for collagen degradation are collagenases, gelatinaseses and elastases. They cause degradation of osseous and connective tissue (85,86). These proteins are characterized by faster destruction of newly formed molecules, which finally results in a lack of new and predominance of old, AGE-containing collagen molecules.

A decrease in collagenase production can be achieved by tetracycline therapy (85,87,88), by using small doses of chemically modified tetracyclines (CMT) that do not seem to have an antibacterial effect (89-91). Their use in diabetic patients has not yet been described.

**Influence of periodontitis on glycemic control in diabetics**

Taylor et al. (92) reported that initially severe periodontitis presents a six times greater risk of poor glycemic control during recall. In a case-controlled study of adult DM patients with gingivitis and mild periodontitis, and patients with DM and severe periodontitis (93), it was reported that subjects with severe periodontitis had significantly greater prevalence of cardiovascular and renal complications in 1 to 11 years, inspite of the fact that haemoglobin A1c (HbA1c) values were similar - i.e the same glycemic control. It seems that classic complications of DM stand in close relationship with periodontitis, and it is reasonable to speak of periodontitis as "the sixth complication of DM" (94). The most difficult question that is yet to be answered in the future is whether the treatment of periodontal disease, point-
ing to elimination of pathogenic microorganisms, may have a positive effect on glycemic control. It is one of the great tasks in the coming years.

**Periodontitis - a risk factor for preterm low birth weight**

Comprehensive research by Offenbacher et al. (95) has shown that untreated periodontitis in pregnant women represents a risk factor for preterm (pregnancy shorter than 37 weeks) low birth weight (less than 2500 grams) (95). It is considered that preterm low birth weight (PLBW) is indirectly caused by inflammation, mostly by translocation of bacterial products - endotoxins (LPS), and by mother's inflammation mediators (96).

Inflammation increases the values of biologically active molecules such as prostaglandin E$_2$ (PGE$_2$) and tumor necrosis factor (TNF-α), which may be responsible for preterm delivery (97). In a recently published article, sulcular PGE$_2$ values were in concordance with intra-amniotic values of PGE$_2$. It may be possible that periodontal inflammation, caused by gram-negative bacteria, suffices to cause preterm delivery, being the source of LPS and/or by stimulating secondary inflammatory mediators, PGE$_2$ and Interleukin-1β (IL-1β) (98). Most recent data suggests a correlation between intrasucular PGE$_2$ as a marker of existing periodontal disease and a decrease in the birth weight of infants. Additionally, it has been established that mothers with PLBW had higher concentrations of four bacterial species that are connected to plaque and periodontitis (*Bacteroides forsythus*, *Porphyromonas gingivalis*, *Actinobacillus actinomycetemcomitans* and *Treponema denticola*), when compared to healthy controls (99).

**Conclusion**

Dentists are more often able to contribute to the improvement and maintenance of general health of their patients. New, evidence-based, advances in periodontology, and in general medical specialities, clearly show a relationship between oral and systemic diseases. However periodontology must explain a multitude of unclear, or insufficiently clear phenomena which will be a priority of science in forthcoming years.