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## Periodontal Inflammation as Risk Factor for Pancreatic Diseases

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### 1. Introduction

During past decades the relationship between dentistry and internal medicine has been intensely debated. Current evidence suggests that inflammation due to periodontal infections may not be limited to the immediate oral environment but can have systemic effects. Clinical, epidemiological and molecular studies have demonstrated significant association between periodontitis and various diseases, such as coronary heart disease, atherosclerosis, bacterial pneumonia, diabetes mellitus and low birth weight. Individuals with periodontal infections have elevated concentrations of circulating inflammatory markers, disease severity directly correlates with serum concentrations of inflammatory markers, and treatment of periodontal infection can lower markers of systemic inflammatory dysfunction within 2–6 months.

Various hypotheses, including common susceptibility, systemic inflammation, direct bacterial infection and cross-reactivity, or molecular mimicry, between bacterial antigens and self-antigens, have been postulated to explain these relationships. In this scenario, the association of periodontal disease with systemic diseases has set the stage for introducing the concept of periodontal medicine.

At present it is generally agreed on that oral status is connected with systemic health, since poor oral health may occur concomitantly with more serious underlying diseases and/or it may predispose to other systemic diseases. The pioneering approach of periodontal medicine has helped to renew attention on the theory of focal infection and the deepening of the relationship between chronic periodontitis and systemic health.

In recent years, chronic periodontitis has been proposed as a risk factor for pancreatic cancer. Chronic periodontitis might promote pancreatic carcinogenesis, by means of systemic inflammation, or alternatively, through increased production of carcinogens, namely nitrosamines.

The aim of the present study was to investigate pancreatic tissue for the potential presence of periodontopathogenic microorganisms.

## 2. Periodontal diseases

Periodontal diseases are a group of bacterial inflammatory diseases of the supporting tissues of the teeth (gingiva, periodontal ligament, cementum and alveolar bone). Periodontal diseases include two general conditions based on whether there is attachment or bone loss: gingivitis and periodontitis. Gingivitis is considered a reversible form of the disease, and generally involves inflammation of the gingival tissues without loss of connective tissue attachment. Gingivitis is the most common and prevalent form of periodontal disease among children and adolescents. The incidence and severity increase from childhood to adolescence, reaching a peak prevalence of 80% at 11-13 years of age. The progression from gingivitis to periodontitis is characterized by periodontal pocket development, which favours further plaque accumulation and a shift in its qualitative composition. Thereafter, as the severity of gingivitis decreases, chronic periodontitis measured by attachment loss becomes dominant and continues to increase in severity with age. Periodontitis is a chronic infection involving destruction of tooth-supporting tissues, including the periodontal ligament and alveolar socket support of the teeth. Periodontal disease can affect one tooth or many teeth and, if left untreated, can lead to tooth loss, particularly in adults. It is the most common dental condition in adults, and is also one of the most common chronic inflammatory diseases affecting a majority of the population throughout the world. Some of the clinical signs include bleeding on probing, deep pockets, recession and tooth mobility. Progressive changes from healthy gums to necrotizing periodontitis are given in Figures 1 to 5.



Fig. 1. Healthy gums

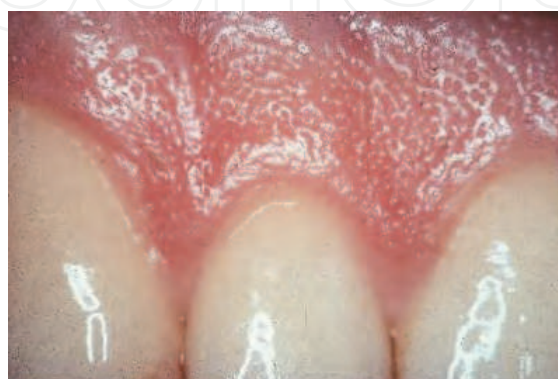


Fig. 2. Gingivitis

## 2.1 Classification of periodontal diseases

### 2.1.1 Chronic periodontitis

Chronic periodontitis is the most common form of periodontitis in adults, but can occur at any age. Progression of attachment loss usually occurs slowly, but periods of exacerbation with rapid progression, or periods of remission can occur. The rate of disease progression may be influenced by local (subgingivally placed fillings or crowns, tooth caries...) and/or systemic conditions (diabetes mellitus, pregnancy, puberty, leukemia...) that alter the normal host response to bacterial plaque. The severity of disease can be described as slight, moderate, or severe, based on the level of destruction.

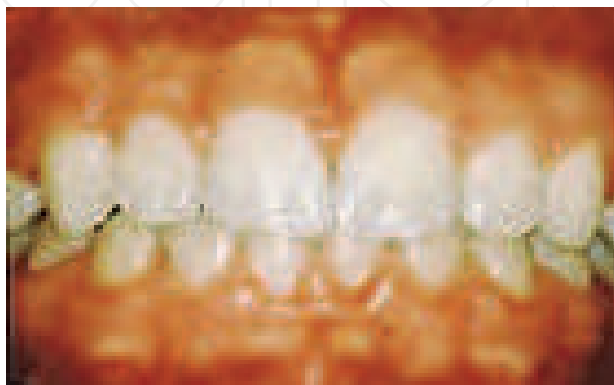


Fig. 3. Gingivitis



Fig. 4. Periodontitis

### 2.1.2 Aggressive periodontitis

Aggressive periodontitis (previously Juvenile Periodontitis) is characterized by rapid attachment loss and bone destruction in the absence of significant accumulations of plaque and calculus. (Tonetti&Mombelly, 1999) This form of periodontitis usually affects young individuals, often during puberty, from 10-30 years of age, with genetic predisposition. The bacteria most often associated with aggressive periodontitis is *Aggregatibacter actinomycetemcomitans* (previously *Actinobacillus actinomycetemcomitans*). Aggressive periodontitis can occur as localized or generalized forms. The localized form usually affects first molar and incisor sites. The generalized form usually involves at least three teeth other than first molars and incisors.

### 2.1.3 Periodontitis as a manifestation of systemic diseases

Periodontitis as a manifestation of systemic diseases may be associated with diabetes, several hematological (acquired, familial, and cyclic neutropenias, leukemias) and genetic disorders (Down's syndrome, certain types of Ehlers-Danlos syndrome, Papillon-Lefevre syndrome, Cohen syndrome and hypophosphatasia). The mechanisms by which all of these disorders affect the health of periodontium are not fully understood, but it is speculated that these diseases can alter host defense mechanisms and upregulate inflammatory responses, resulting in progressive periodontal destruction.

### 2.1.4 Necrotizing periodontal diseases

Necrotizing periodontal diseases (necrotizing gingivitis, necrotizing periodontitis and necrotizing stomatitis) are the most severe inflammatory periodontal disorders caused by plaque bacteria. These lesions are commonly observed in individuals with systemic conditions such as HIV infection, malnutrition and immunosuppression. Clinical characteristics of necrotizing periodontal diseases may include but are not limited to ulcerated and necrotic papillary and marginal gingiva covered by a yellowish and grayish slough or pseudomembrane, blunting and cratering of papillae, bleeding on provocation or spontaneous bleeding, pain, and fetid breath. These diseases may be accompanied by fever, malaise, and lymphadenopathy, although these characteristics are not consistent.



Fig. 5. Necrotizing periodontitis

These diseases appear to have multiple etiologies, microbial and immunological being the two most studied. The primary microbial factor contributing to disease is a shift in the content of the oral microflora, while the primary immunological factor is the destructive host inflammatory response.

## 2.2 Microbial etiology of periodontal disease

As many as 700 different species of bacteria that colonize the oral cavity can affect the delicate balance of host-bacterial interactions leading to disease. Periodontal infection is initiated by specific invasive oral pathogens that colonize dental plaque biofilms on the



tooth root surface. No one knows how many bacterial species, ribotypes, and serotypes coexist in the dental plaque, but the number is very large. With the advent of PCR technologies, many new uncultivable species are being identified.

The onset and progression of periodontal disease is attributed to the presence of elevated levels of a consortium of pathogenic bacteria within the gingival crevice. The plaque is divided into two distinct types based on the relationship of the plaque to the gingival margin, i.e., supragingival plaque and subgingival plaque. The supragingival plaque is dominated by facultative *Streptococcus* and *Actinomyces* species, whereas the subgingival plaque harbors an anaerobic gram-negative flora dominated by uncultivable spirochetal species. It is this gram-negative flora that has been associated with periodontal disease. Since many of its members derive some of their nutrients from the gingival crevicular fluid, a tissue transudate that seeps into the periodontal area, it is possible that their overgrowth is a result of the inflammatory process (Loe et al., 1965).

The disease is a chronic low grade infection involving mainly Gram-negative anaerobic bacteria. There is a clear evidence for the pathogenic role of *Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis* and *Tannerella forsythia* in periodontal disease development and a reasonably strong evidence exists for the pathogenic role in certain forms of periodontal disease of some other microorganisms such as *Prevotella intermedia*, *Fusobacterium nucleatum*, *Campylobacter rectus*, *Eikenella corrodens* etc (Brajovic et al., 2010; Milicevic et al, 2008). A number of gram-negative rods and spirochetes are putative periodontal pathogens, but these organisms may also be present, although in smaller concentrations, in healthy patients.

Although the plaque is essential for the initiation of periodontal diseases, the majority of the destructive processes associated with these diseases are due to an excessive host response to the bacterial challenge. Periodontal bacteria possess a plethora of virulence factors that, upon interaction with host cells, induce the production of inflammatory mediators at the gingival level.

### 2.3 Host inflammatory response to bacterial challenge

The fundamental question in regard to periodontal pathology is whether the host is responding to the nonspecific overgrowth of bacteria on the tooth surfaces (inflammatory disease) or to the overgrowth of a limited number of species which produce biologically active molecules that are particularly proinflammatory or antigenic (infection).

There is a distinction between the way the host responds to the supragingival plaque and its response to the subgingival plaque. The response to the supragingival plaque has been thoroughly studied in the experimental gingivitis model described below, whereas the response to the subgingival plaque remains under investigation. Does the host respond to the subgingival plaque as if it were an overgrowth of a bacterial community in which many members produce substances, such as LPS, that are particularly bioactive if they enter the gingival tissue? Or does it respond to a plaque in which certain members produce more biologically active molecules, such as butyric acid (Niederman al., 1997) or hydrogen sulfide (Ratcliff&Johnson, 1999), per cell or possess unique proteases, such as are found in *P. gingivalis* and *Treponema denticola*, which can degrade host molecules, creating a proinflammatory effect (Kuramitsu, 1998)? In either case, although bacteria are involved, it is not the scenario of a typical infection, as the offending bacteria generally remain outside the body, attached to the tooth.

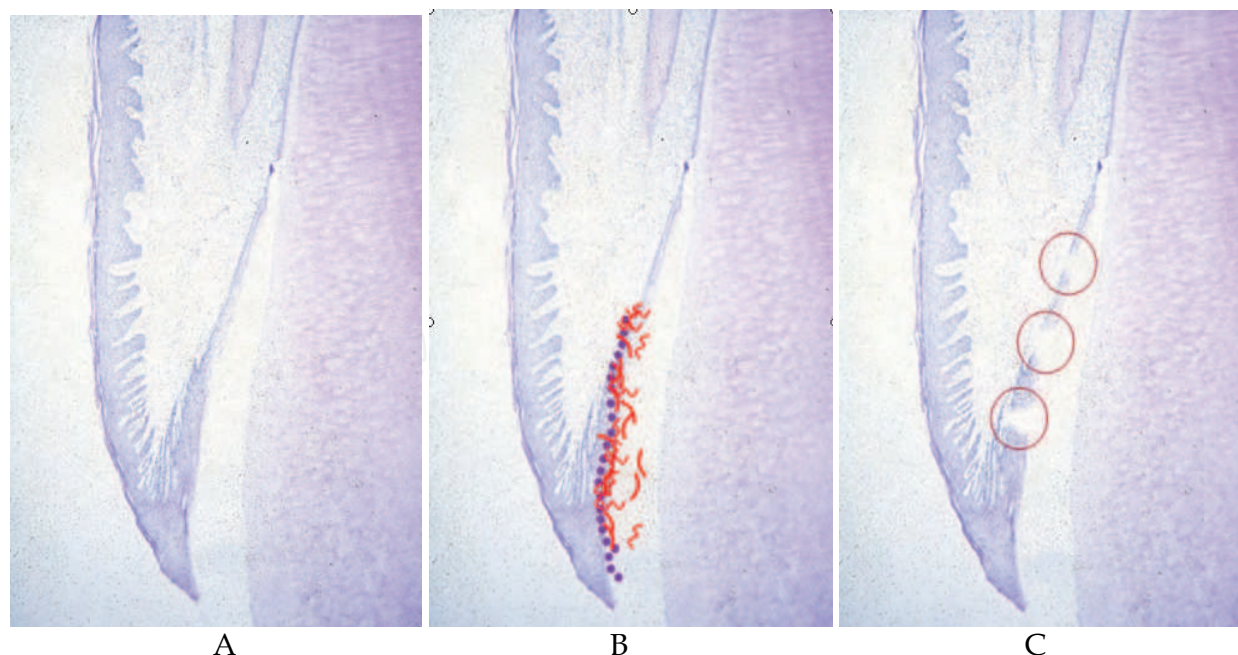


Fig. 6. A) Histology of normal gingiva; B) Accumulation of Gram positive and Gram negative bacteria and bacterial toxins; C) Basement membrane and tissue destruction leading to epithelial ulcerations.

In periodontal disease the inflammatory response causes tissue resistance to bacterial invasion but also provides mechanisms that contribute to tissue damage. Acute inflammatory cells, such as mast cells, macrophages, Langerhans cells, and polymorphonuclear leukocytes, combine their action to form a potent antibacterial defense mechanism. However the initial signs of gingival inflammation (swelling, redness, bleeding on probing) are nothing but the tissue-destructive aspects of the activity of these cells. Neutrophils function to control the bacterial assault by phagocytosis but also secrete matrix metalloproteinases (MMP), which are the agents responsible for collagen loss in the tissues. These latent collagenolytic enzymes can be converted to active forms by proteases and reactive oxygen species in the inflammatory environment, giving rise to elevated levels of interstitial collagenase in the inflamed gingival tissue. The resulting attachment loss deepens the sulcus, or depression, formed where the gingival tissues contact the tooth surface, thereby creating the periodontal pocket. By definition, this loss of attachment converts gingivitis to periodontitis. The depth of the pocket reflects an inflammatory response that causes both the swelling of the gingival tissues at the top of the pocket and the loss of collagen attachment of the tooth to the alveolar bone at the bottom of the pocket. Good oral hygiene can reduce the inflammatory swelling, but the attachment loss and accompanying bone loss is thought to be irreversible. In established periodontal disease, there is also a chronic inflammatory change, with B cells and T cells adding to the antibacterial spectrum. These cells also have capacity to release cytokines, which may induce the synthesis of arachidonate metabolites (especially PGE<sub>2</sub>), and to stimulate macrophages and osteoclasts to release hydrolases and collagenases, which are responsible for loss of collagen and bone. The interaction of bacterial antigens with peripheral dendritic cells leads to the generation of systemic antibody, whereas interaction with local B cells leads to production of local antibody. Antibody specific to many of the periodontal

microorganisms is essential for phagocytosis. Complement components also may contribute to efficient bacterial phagocytosis. The production of interleukin-1 $\beta$  (IL-1 $\beta$ ), tumor necrosis factor alpha (TNF- $\alpha$ ), and prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) in response to bacterial lipopolysaccharides (LPS) leads to bone resorption through osteoclast activation, proliferation, and differentiation. Each patient with dental plaque has a complex balance between these protective and damaging scenarios that results either in a slowly progressive loss of attachment (periodontitis) or in a restriction of tissue inflammation to the peripheral tissues (gingivitis).

## **2.4 Treatment of periodontal disease**

Various treatment modalities, such as the traditional debridement procedures (scaling and root planning), surgery (Kwan et al., 1998; Lekovic et al., 1997, 1998a, 1998b, 2001a, 2001b, 2003, 2005; Camargo et al., 1998, 2000, 2002, 2005) and various antimicrobial regimens were introduced for the treatment of periodontal disease.

Traditional treatments reflect the premise that periodontal disease is due to the nonspecific overgrowth of any and all bacteria on the tooth surfaces and that the magnitude of the bacterial overgrowth on the teeth can be controlled by professional cleaning of the teeth at regular intervals. If these accumulations are not removed, various bacterial by-products and their cellular components such as LPS, antigens, or enzymes can provoke an inflammatory response in the gingival tissue. Undisturbed plaques often become calcified, forming dental calculus or tartar, which, if formed below the gingival margin, is often difficult to remove from the root surfaces without some form of surgical access.

This type of periodontal treatment which is considered to be the standard treatment, is based on the premise that if the bacterial overgrowth in dental plaque can be continuously suppressed by mechanical debridement, gingival and periodontal health will be maintained. It is the basis of the “plaque control” programs of organized dentistry and dentifrice manufacturers; as a public health effort, this approach has been very successful.

## **3. Oral-systemic relationship**

In the last decade, the possible association between oral and systemic health has been highlighted in numerous reports. Apart from the seeding infection as a direct consequence of transient bacteraemia, such oral-systemic interactions and outcomes could be due to other, indirect reasons, such as metastatic inflammation as a result of circulating macromolecular complexes and/or metastatic injury due to soluble toxins and bacterial lipopolysaccharide. It has become increasingly clear that the oral cavity can act as the site of origin for dissemination of pathogenic organisms to distant body sites, especially in immunocompromised hosts such as patients suffering from malignancies, diabetes, or rheumatoid arthritis or having corticosteroid or other immunosuppressive treatment. A number of epidemiological studies have suggested that oral infection, especially marginal and apical periodontitis, may be a risk factor for systemic diseases.

### **3.1 Transient bacteraemia**

In common inflammatory conditions such as gingivitis and chronic periodontitis, which are precipitated by the buildup of plaque biofilms, the periodontal vasculature proliferates and



dilates, providing an even greater surface area that facilitates the entry of microorganisms into the bloodstream. Often, these bacteraemias are short-lived and transient, with the highest intensity limited to the first 30 min after a trigger episode. On occasions, this may lead to seeding of microorganisms in different target organs, resulting in subclinical, acute, or chronic infections. Yet there are a number of other organs and body sites that may be affected by focal bacteremic spread from the oral cavity. Based on the current evidence, it is likely that bacteria may enter into the bloodstream from oral niches through a number of mechanisms and a variety of portals. First, and most commonly, when there is tissue trauma induced by procedures such as periodontal probing, scaling, instrumentation beyond the root apex, and tooth extractions, a breakage in capillaries and other small blood vessels that are located in the vicinity of the plaque biofilms may lead to spillage of bacteria into the systemic circulation. As stated above, dissemination of oral microorganisms into the bloodstream is common, and less than 1 minute after an oral procedure, organisms from the infected site may have reached the heart, lungs, and peripheral blood capillary system. There are more than  $10^{13}$  microbes on all surfaces of the body, yet the underlying tissues and the bloodstream are usually sterile. In the oral cavity there are several barriers to bacterial penetration from dental plaque into the tissue: a physical barrier composed of the surface epithelium; defensins, which are host-derived peptide antibiotics, in the oral mucosal epithelium; an electrical barrier that reflects the difference between the host cell and the microbial layer; an immunological barrier of antibody-forming cells; and the reticuloendothelial system (phagocyte barrier). Under normal circumstances, these barrier systems work together to inhibit and eliminate penetrating bacteria. When this state of equilibrium is disturbed by an overt breach in the physical system (e.g., trauma), the electrical system (i.e., hypoxia), or immunological barriers (e.g., through neutropenia, AIDS, or immunosuppressant therapy), microorganisms can propagate and cause both acute and chronic infections with increased frequency and severity. With normal oral health and dental care, only small numbers of mostly facultative bacterial species gain access to the bloodstream. However, with poor oral hygiene, the numbers of bacteria colonizing the teeth, especially supragingivally, could increase 2- to 10-fold and thus possibly introduce more bacteria into tissue and the bloodstream, leading to an increase in the prevalence and magnitude of bacteraemia.

Obviously, a higher microbial load would facilitate such dissemination, as it is known that individuals with poor oral hygiene are at a higher risk of developing bacteraemias during oral manipulative procedures. Innate microbial factors may play a role in the latter phenomenon, as only a few species are detected in experimental bacteraemias despite the multitude of diverse bacteria residing within the periodontal biofilm. Species that are commonly found in the bloodstream have virulence attributes that could be linked to vascular invasion. Of particular note are attributes such as endothelial adhesion of *Streptococcus* spp., degradation of intercellular matrices by *Porphyromonas gingivalis*, and impedance of phagocytic activity by *Aggregatibacter actinomycetemcomitans* and *Fusobacterium nucleatum*. As opposed to the more than 700 bacterial species that inhabit the oral cavity, relatively fewer species have been isolated from blood cultures for odontogenic bacteraemias. Phylogenetic studies of the oral microbiome have shown that a large proportion of the oral bacteria comprise the genus *Streptococcus* (Van Dyke et al., 1982.). In a number of controlled clinical trials, streptococci were the predominant organisms isolated,

ranging from 40 to 65% of isolates. The highest incidence of bacteraemia results from tooth extractions. Periodontal manipulations are also shown to produce a long-lasting (30 min) bacteraemia. This is probably a reflection of the bacterial load and tissue trauma or associated inflammation at these niches. Other oral procedures are not as significant, at least for individuals with healthy oral cavities. Routine oral hygiene measures such as brushing or flossing are unlikely to cause a significant degree of bacteraemia, but sporadic cleaning after accumulation of a heavy plaque load should be considered a potential risk factor for a bacteremic state.

### **3.2 Mechanisms linking oral infection to secondary nonoral diseases**

Three mechanisms or pathways linking oral infections to secondary systemic effects have been proposed. These are metastatic spread of infection from the oral cavity as a result of transient bacteraemia, metastatic injury from the effects of circulating oral microbial toxins, and metastatic inflammation caused by immunological injury induced by oral microorganisms.

#### **3.2.1 Metastatic infection**

As previously discussed, oral infections and dental procedures can cause transient bacteraemia. The microorganisms that gain entrance to the blood and circulate throughout the body are usually eliminated by the reticuloendothelial system within minutes (transient bacteraemia) and as a rule lead to no other clinical symptoms than possibly a slight increase in body temperature. However, if the disseminated microorganisms find favorable conditions, they may settle at a given site and, after a certain time lag, start to multiply.

#### **3.2.2 Metastatic injury**

Some gram-positive and gram-negative bacteria have the ability to produce diffusible proteins, or exotoxins, which include cytolytic enzymes and dimeric toxins. The exotoxins have specific pharmacological actions and are considered the most powerful and lethal poisons known (51). Conversely, endotoxins are part of the outer membranes released after cell death. Endotoxin is compositionally a lipopolysaccharide (LPS) that, when introduced into the host, gives rise to a large number of pathological manifestations. LPS is continuously shed from periodontal gram-negative rods during their growth *in vivo*.

#### **3.2.3 Metastatic inflammation**

Soluble antigen may enter the bloodstream, react with circulating specific antibody, and form a macromolecular complex. These immunocomplexes may give rise to a variety of acute and chronic inflammatory reactions at the sites of deposition.

## **4. Periodontitis affects susceptibility to systemic disease**

In a recent review article, Page proposed that periodontitis may affect the host's susceptibility to systemic disease in three ways: by shared risk factors, by subgingival biofilms acting as reservoirs of gram-negative bacteria, and through the periodontium acting as a reservoir of inflammatory mediators.

#### 4.1 Shared risk factors

Factors that place individuals at high risk for periodontitis may also place them at high risk for systemic diseases such as cardiovascular disease. Among the environmental risk factors and indicators shared by periodontitis and systemic diseases, such as cardiovascular disease, are tobacco smoking, stress, aging, race or ethnicity, and male gender. Studies demonstrating genetic factors shared by periodontitis, cardiovascular disease, preterm labor, and osteoporosis have not yet been performed but may be fruitful.

#### 4.2 Subgingival biofilms

Subgingival biofilms constitute an enormous and continuing bacterial load. They present continually renewing reservoirs of LPS and other gram-negative bacteria with ready access to the periodontal tissues and the circulation. Systemic challenge with gram-negative bacteria or LPS induces major vascular responses, including an inflammatory cell infiltrate in the vessel walls, vascular smooth muscle proliferation, vascular fatty degeneration, and intravascular coagulation. LPS upregulates expression of endothelial cell adhesion molecules and secretion of interleukin-1 (IL-1), tumor necrosis factor alpha (TNF- $\alpha$ ), and thromboxane, which results in platelet aggregation and adhesion, formation of lipidladen foam cells, and deposits of cholesterol and cholesterol esters.

#### 4.3 Periodontium as cytokine reservoir

The proinflammatory cytokines TNF- $\alpha$ , IL-1 $\beta$ , and gamma interferon as well as prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) reach high tissue concentrations in periodontitis. The periodontium can therefore serve as a renewing reservoir for spillover of these mediators, which can enter the circulation and induce and perpetuate systemic effects. IL-1 $\beta$  favors coagulation and thrombosis and retards fibrinolysis. IL-1, TNF- $\alpha$ , and thromboxane can cause platelet aggregation and adhesion, formation of lipidladen foam cells, and deposition of cholesterol. These same mediators emanating from the diseased periodontium may also account for preterm labor and low-birth-weight infants (Page, 1998).

### 5. Cardiovascular disease

Cardiovascular disease and periodontal disease are both chronic inflammatory diseases. Numerous cross-sectional and longitudinal epidemiological studies have provided evidence that there is an association between periodontitis and elevated risk for cardiovascular disease. A number of systematic reviews and meta-analyses have described the relationship between periodontal infection and cardiovascular disease, and have suggested that periodontitis may contribute to cardiovascular disease and stroke in susceptible subjects.

It is well accepted that hyperlipidemia is a risk factor for coronary heart disease. Recent studies have shown an association between periodontitis and elevated atherogenic lipid fraction levels and / or decreased anti-atherogenic lipid fraction levels. Most of these were cross-sectional studies, and it is still unclear whether there is a causal relationship between periodontitis and hyperlipidemia. Improvement of serum lipid profiles after periodontal treatment may indicate a causal relationship between periodontitis and hyperlipidemia, and may suggest the possibility of reducing the risk of coronary heart disease by effective periodontal intervention.

C-reactive protein is an important marker for systemic inflammation, and has been consistently found to be elevated in patients with coronary syndromes. Recently, evidence

has accumulated demonstrating the association between periodontitis and C-reactive protein. The serum C-reactive protein concentration is increased in systemically healthy subjects with periodontitis. Numerous studies indicate that periodontal intervention therapy may decrease the C-reactive protein-associated cardiovascular disease risk.

Many cytokines play a role in the pathogenesis of both coronary heart disease and periodontitis. These include interleukin-1, interleukin-6, interleukin-8, tumor necrosis factor- $\alpha$ , intercellular adhesion molecule-1 (ICAM-1), P-selectin and E-selectin. Some intervention studies have indicated that periodontal therapy can reduce the levels of these pro-inflammatory cytokines, and thus periodontal treatment may lower the cardiovascular disease risk.

Numerous studies of different design and rigor have provided statistical evidence for an association between periodontal disease and cardiovascular disease, raising the possibility that periodontal disease is a risk factor for cardiovascular disease. There are several proposed mechanisms (Fig. 1) by which periodontal disease may trigger pathways leading to cardiovascular disease through direct and indirect effects of oral bacteria. First, evidence indicates that oral bacteria such as *Streptococcus sanguis* and *Porphyromonas gingivalis* induce platelet aggregation, which leads to thrombus formation. These organisms have a collagen-like molecule, the platelet aggregation-associated protein, on their surface. Furthermore, one or more periodontal pathogens have been found in 42% of the atheromas studied in patients with severe periodontal disease (Zambon, 1998). The second factor in this process could be an exaggerated host response to a given microbial or LPS challenge, as reflected in the release of high levels of proinflammatory mediators such as PGE<sub>2</sub>, TNF- $\alpha$ , and IL-1 $\beta$ . These mediators have been related to interindividual differences in the T-cell repertoire and the secretory capacity of monocytic cells. Typically, peripheral blood monocytes from these individuals with the hyperinflammatory monocyte phenotype secrete 3- to 10-fold-greater amounts of these mediators in response to LPS than those from normal monocyte phenotype individuals. Patients with certain forms of periodontal disease, such as early-onset periodontitis and refractory periodontitis, possess a hyperinflammatory monocyte phenotype. A third mechanism possibly involves the relationship between bacterial and inflammatory products of periodontitis and cardiovascular disease. LPS from periodontal organisms being transferred to the serum as a result of bacteraemias or bacterial invasion may have a direct effect on endothelia so that atherosclerosis is promoted (Pesonen et al., 1981). LPS may also elicit recruitment of inflammatory cells into major blood vessels and stimulate proliferation of vascular smooth muscle, vascular fatty degeneration, intravascular coagulation, and blood platelet function. These changes are the result of the action of various biologic mediators, such as PGs, ILs, and TNF- $\alpha$  on vascular endothelium and smooth muscle. Fibrinogen and WBC count increases noted in periodontitis patients may be a secondary effect of the above mechanisms or a constitutive feature of those at risk for both cardiovascular disease and periodontitis (Kweider et al., 1993).

If so, periodontal disease, because it is both preventable and treatable, becomes a modifiable risk factor for cardiovascular disease. However, if periodontal disease is primarily due to the overgrowth of bacteria in the dental plaque, all individuals would need preventive treatment, since all individuals form dental plaque.

### 5.1 Atherosclerosis

Atherosclerosis has been defined as a progressive disease process that involves large- to medium-sized muscular and large elastic arteries. The advanced lesion is the atheroma,



which consists of elevated focal intimal plaques with a necrotic central core containing lysed cells, cholesterol ester crystals, lipid-laden foam cells, and surface plasma proteins, including fibrin and fibrinogen. In the last few years there were an increasing number of reports dealing with the possible relationship between atherosclerosis and periodontitis, as well as between chronic coronary heart disease and periodontitis (Fien et al., 2005; Ford et al., 2006; Pucar et al., 2007; Spahr et al., 2006). Arteries have been thoroughly explored for the presence of periodontopathogens and a variety of oral microorganisms have been found lodged in arterial walls.

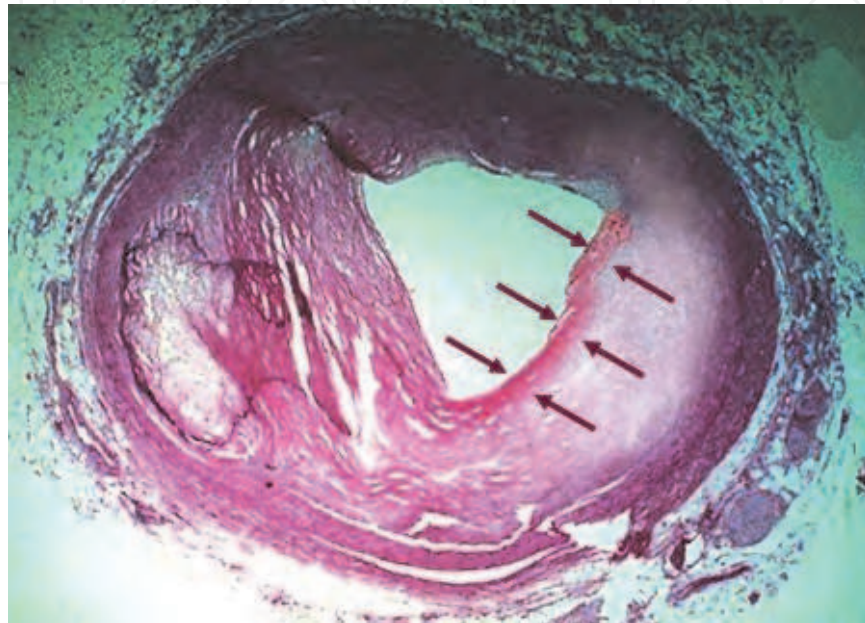


Fig. 7. Coronary artery with stable atheroma. Inflammation and necrosis have replaced the smooth muscle but there is a dense layer of collagen next to lumen (arrows)

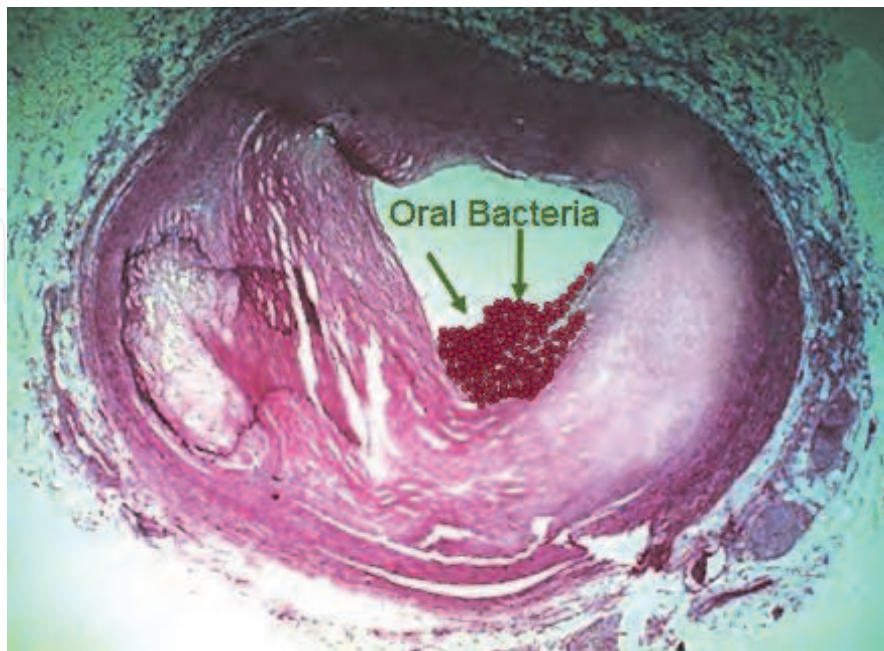


Fig. 8. Circulating oral bacteria have peptides that cause platelet aggregation (arrows)

There are sufficient data to consider that *A.actinomycetamcomitans*, *P. gingivalis* and *P. intermedia* have the ability to invade host cells including epithelium and endothelium evading the neutrophil clearance; in this way periodontal pathogens can penetrate the epithelial barrier of the periodontal tissues and get systemic spreading through the blood stream. By this dynamic, periodontal pathogens can infect directly the vascular endothelium, and atherosclerotic plaques, causing inflammation and plaque instability up to an acute myocardial ischemia. Moreover, periodontal pathogens produce a variety of virulence factors (e.g. adhesions, portliness, haemolysins, membrane vesicles and LPS) that have deleterious effects on vascular system, resulting in platelet aggregation and adhesion, formation of lipid-laden foam cells and deposits of cholesterol, all factors contributing to the formation of atheroma.

Endothelial dysfunction is a fundamental step in the development of atherosclerosis, and can be measured by several methods, including flow-mediated dilatation of the brachial artery. Endothelial dysfunction as determined by measurement of brachial flow-mediated dilatation is considered to be a good predictor of cardiovascular outcomes (Roquer et al., 2009).

Periodontal disease is associated with endothelial dysfunction as measured by brachial flow-mediated dilatation. Endothelial function has been reported to be significantly lower in patients with periodontitis than in control subjects. In addition, endothelial dysfunction in hypertensive patients with periodontitis is more severe compared to hypertensive patients without periodontitis (Higashi et al., 2009). Recently, endothelial function was evaluated in healthy and periodontitis patients with coronary artery disease (Higashi et al., 2008). The results showed that endothelial function was significantly lower in the periodontitis group with coronary artery disease than in the nonperiodontitis group with coronary artery disease. These results suggest that periodontitis is a contributor to endothelial dysfunction, and hence could increase the risk of cardiovascular disease. Based on current evidence, periodontal therapy can improve endothelial dysfunction in periodontitis patients whether they are systemically healthy or have hypertension. This further confirms the causal association between periodontitis and endothelial dysfunction. As endothelial dysfunction is associated with an adverse prognosis for atherosclerosis and cardiovascular disease, periodontal intervention therapy may bring benefits to patients with periodontitis by improving endothelial function, thus reducing the risk of cardiovascular disease. However, this requires further study.

## 6. Diabetes mellitus

Recent findings indicate that oral health may influence systemic health, and that this may be a bi-directional relationship for some conditions. This is particularly true for the relationship between periodontal disease and diabetes mellitus. The inter-relationship between periodontal disease and diabetes mellitus provides an example of a cyclic association, whereby a systemic disease predisposes the individual to oral infections, and, once the oral infection is established, it exacerbates the systemic disease.

The inflammatory response in the periodontal tissues in response to challenge by dental biofilm is complex and involves networks of cytokines functioning in synergy. The inflammatory response is characterized by localized production of various inflammatory markers and enzymes, such as C-reactive proteins, cytokines (interleukin-1b, interleukin-6, tumor necrosis factor  $\alpha$ ), prostanoids (prostaglandin E2) and matrix metalloproteinases.

These increased secretions of inflammatory cytokines contribute to bone loss in periodontitis. The balance between the protective host factors and microbial challenge is greatly influenced by environmental and genetic factors that have an impact on the immuno-inflammatory response of the host. Alterations in immunologically active molecules as a result of diabetes may alter the levels of cytokines in the periodontium, which accelerates progression of the disease. This is the scientific basis for the increased susceptibility to periodontal disease seen in diabetics.

Patients with diabetes exhibited greater periodontal breakdown in response to dental biofilm; however, this depended on the degree of glycemic control (Arrieta-Blanco et al., 2003; Bastard et al., 2006). The highest levels of gingivitis were seen in diabetic patients with poor glycemic control (Mealey, 2006). Clinical and epidemiological studies have reported a higher prevalence and increased severity of periodontal disease in diabetic patients compared with non-diabetic controls (Ciancola et al., 1982; Collin et al., 1998; Safkan-Seppala et al., 1992). Studies have shown that diabetes carries a threefold increased risk of periodontitis compared to non-diabetic individuals (Lo'e et al., 1978; Slossman et al., 1990). Alveolar bone loss is enhanced in these individuals, resulting in a more persistent inflammatory response in diabetics. This leads to greater attachment loss and impaired formation of new bone (Liu et al., 2006). In addition, Lo'e (Lo'e, 1993) described periodontitis as the 6th complication of diabetes, together with retinopathy, nephropathy, neuropathy, macrovascular diseases and altered wound healing. The complications of diabetes are related to long-term elevation of blood glucose concentrations (hyperglycaemia) that results in the formation of advanced glycation end-products (AGEs). The accumulation of AGEs increases the intensity of the immune-inflammatory response to different pathogens, because inflammatory cells such as monocytes and macrophages have receptors for AGEs with consequent increased production of IL-1 $\beta$  and TNF- $\alpha$ . The AGEs-enriched gingival tissue has greater vascular permeability, greater breakdown of collagen fibers and accelerated destruction of both non-mineralized connective tissue and bone occurs. Diabetes can also cause damage of neutrophil adhesion, chemotaxis and phagocytosis, making patients more susceptible to periodontal destruction. The effects of the hyperglycemic state include the inhibition of osteoblastic proliferation and collagen production. Several studies indicated that diabetes is associated with an increased prevalence, extent and severity of chronic periodontitis. Other studies have suggested that the presence of periodontal infection may be linked to poor metabolic control of diabetes (Southerland et al., 2005). Treatment of periodontal disease can alter glycemic control, and early intervention and treatment of periodontitis may help to prevent the long-term complications of diabetes, thereby having an impact on mortality.

## 7. Bacterial pneumonia

Pneumonia is an infection of pulmonary parenchyma caused by a wide variety of infectious agents, including bacteria, fungi, parasites, and viruses. Pneumonia can be a life-threatening infection, especially in the old and immunocompromised patient, and is a significant cause of morbidity and mortality in patients of all ages. Most commonly, bacterial pneumonia results from aspiration of oropharyngeal flora into the lower respiratory tract, failure of host defense mechanisms to eliminate them, multiplication of the microorganisms, and subsequent tissue destruction. It is likely that most pathogens first colonize the surfaces of the oral cavity or pharyngeal mucosa before aspiration. These pathogens can colonize from



an exogenous source or emerge following overgrowth of the normal oral flora after antibiotic treatment. Common potential respiratory pathogens (PRPs) such as *Streptococcus pneumoniae*, *Mycoplasma pneumoniae*, and *Haemophilus influenzae* can colonize the oropharynx and be aspirated into the lower airways. Other species thought to comprise the normal oral flora, including *A. actinomycetemcomitans* and anaerobes such as *P. gingivalis* and *Fusobacterium* species, can also be aspirated into the lower airways and cause pneumonia. Pneumonia can result from infection by anaerobic bacteria. Dental plaque would seem to be a logical source of these bacteria, especially in patients with periodontal disease. Such patients harbor a large number of subgingival bacteria, particularly anaerobic species. Among the oral bacterial species implicated in pneumonia are *A. actinomycetemcomitans*, *Actinomyces israelii*, *Capnocytophaga* spp., *Eikenella corrodens*, *Prevotella intermedia*, and *Streptococcus constellatus*. A study has shown that individuals with respiratory disease have significantly higher oral hygiene index scores than subjects without respiratory disease.

## 8. Low birth weight

Pregnancy can influence gingival health. Changes in hormone levels during pregnancy promote an inflammation termed pregnancy gingivitis. This type of gingivitis may occur without changes in plaque levels. Oral contraceptives may also produce changes in gingival health. Some birth control pill users have a high gingival inflammation level but a low plaque level. Birth control pills may cause changes such as alteration of the microvasculature, gingival permeability, and increased synthesis of estrogen.

Oral infections also seem to increase the risk for or contribute to low birth weight in newborns. Low birth weight, defined as a birth weight of <2,500 g, is a major public health problem in both developed and developing countries. As a remote gram-negative infection, periodontal disease may have the potential to affect pregnancy outcome. During pregnancy, the ratio of anaerobic gram-negative bacterial species to aerobic species increases in dental plaque in the second trimester. The gram-negative bacteria associated with progressive disease can produce a variety of bioactive molecules that can directly affect the host. One microbial component, LPS, can activate macrophages and other cells to synthesize and secrete a wide array of molecules, including the cytokines IL-1b, TNF-a, IL-6, and PGE2 and matrix metalloproteinases. If they escape into the general circulation and cross the placental barrier, they could augment the physiologic levels of PGE2 and TNF-a in the amniotic fluid and induce premature labor.

Human case-control studies have demonstrated that women who have low-birth-weight infants as a consequence of either preterm labor or premature rupture of membranes tend to have more severe periodontal disease than mothers with normal-birth-weight infants. In a recent case-control study, 48 case-control subjects had their gingival crevicular fluid (GCF) levels of PGE2 and IL-1b measured to determine whether mediator levels are related to current pregnancy outcome. In addition, the levels of four periodontal pathogens were measured by using microbespecific DNA probes. The results indicate that GCF PGE2 levels are significantly higher in mothers of preterm low-birthweight infants than in mothers of normal-birth-weight infants (controls). These data suggest a dose-response relationship for increased GCF PGE2 as a marker of current periodontal disease activity and decreasing birth weight. Four organisms associated with mature plaque and progressing periodontitis, *Bacteroides forsythus*, *P. gingivalis*, *A. actinomycetemcomitans*, and *Treponema denticola*, are



detected at higher levels in mothers of preterm low-birth-weight infants than in controls. These data suggest that biochemical measures of maternal periodontal status and oral microbial burden are associated with preterm birth and low birth weight. 18.2% of preterm low-birth-weight babies may result from periodontal disease – a previously unrecognized and clinically important risk factor for preterm birth and low birth weight. The association between periodontal disease and low birth weight may reflect the patient's altered immune-inflammatory trait that places the patient at risk for both conditions.

Thus, periodontitis may be a marker for preterm delivery susceptibility as well as a potential risk factor. Indeed, the data from animal models suggest that even if periodontal disease is not the primary cause of prematurity, in a subset of patients it may serve as a contributor to the condition. Currently, there is insufficient evidence to link chronic periodontitis to specific adverse pregnancy outcomes.

## 9. Cancer associated with chronic inflammation

Various studies confirmed that malignancies may arise from areas of infection and inflammation, simply as part of the normal host response. Indeed, there is a growing body of evidence that many malignancies are initiated by infections (Kuper et al., 2000; Sachter et al., 2002). Persistent infections within the host induce chronic inflammation. Leukocytes and other phagocytic cells induce DNA damage in proliferating cells, through their generation of reactive oxygen and nitrogen species that are produced normally by these cells to fight infection. These species react to form peroxynitrite, a mutagenic agent (Maeda & Akaike, 1998). Hence, repeated tissue damage and regeneration of tissue, in the presence of highly reactive nitrogen and oxygen species released from inflammatory cells, interacts with DNA in proliferating epithelium resulting in permanent genomic alterations such as point mutations, deletions, or chromosomal rearrangements.

More recently, a link between periodontal disease and cancer has been suggested. The scientific rationale behind the proposed association is that inflammation is a major factor in both periodontal disease and cancer.

Oral cancer, gingival squamous cell carcinoma in particular, has been known to mimic advanced periodontal disease in clinical appearance showing similar symptoms of swelling, bleeding, tooth mobility, deep periodontal pockets, and bone destruction. Many cases have been reported of gingival squamous cell carcinoma presenting clinically similar to inflammatory periodontal or periodontal/endodontic lesions. Cases of other types of cancer mistaken for periodontal disease such as metastatic pancreatic cancer and osteogenic sarcoma have also been reported. These examples hint that a similar underlying mechanism may be responsible for both periodontal disease and cancer.

### 9.1 Cancers and periodontal disease

Several hypotheses are of interest in the potential etiology of a link between, periodontal disease and cancer.

#### 9.1.1 Alteration of the oral flora

It has been suggested that carcinogenic metabolic by-products of periodontal disease might account for the relationship between the two diseases. When considering gastric cancers, it

had been argued that the mechanism of increased cancer risk may be an increased production of nitrosamines in situations of poor oral hygiene and that these by-products may function as gastro-intestinal organ specific carcinogens. Nitrosamines have been linked to cancers of the stomach and esophagus. *Helicobacter pylori* infection also plays a role in stomach cancers (Zarić et al, 2009). Other microorganisms have been studied as well as potential carcinogenic agents. There is also evidence that some strains of candidiasis have been seen at higher frequency in oral cancer patients. Viruses may also play a role. A suggestion has been made that increased periodontal disease may be associated with infection with cytomegalovirus and/or Epstein-Barr Virus 1 with mixed results. EBV of course has been linked to cancer including lymphoma and nasopharyngeal carcinoma.

### **9.1.2 Increase in systemic circulatory inflammatory markers**

The presence of inflammatory cells and mediators such as chemokines, cytokines, and prostaglandins represent indicators associated with tumors. Also, the immune response mounted to a chronic periodontal infection has been proposed as a potential carcinogenic etiologic factor. Also of interest is the relationship between the pro-inflammatory expression of the receptor for advanced glycation end products (RAGE) and esophageal, gastric, colon, biliary, pancreatic, and prostate cancers. RAGE has been shown to play a role in the inflammatory processes of oral infections including periodontal disease. There are several obstacles in accurately determining a relationship between, periodontal disease and cancer.

### **9.1.3 Confounding factors**

Smoking appeared to be the main confounding factor among these studies, especially for cancers strongly linked to tobacco use such as lung cancer. Other potential confounding factors are socio-economic status, diabetes, age, gender and ethnicity, along with genetics.

## **9.2 Chronic periodontitis as a risk factor for pancreatic cancer**

Cancer of the pancreas is a rapidly fatal tumor. Smoking is the only well-documented modifiable risk factors for this cancer, although data suggest that diabetes, obesity and insulin resistance are also risk factors. Alcohol consumption is not an established risk factor for pancreatic cancer, but there is a strong association between alcohol consumption and chronic pancreatitis, and the latter has been associated with a higher risk for pancreatic cancer.

Although viral infections have been strongly associated with cancers, several bacteria can promote or initiate abnormal cell growth by evading the immune system or suppressing apoptosis. Since periodontitis is a chronic oral bacterial infection, few authors have suggested a possible positive association between periodontitis and pancreatic cancer. Chronic periodontitis might promote pancreatic carcinogenesis, by means of systemic inflammation, or alternatively, through increased production of carcinogens, namely nitrosamines. Nitrosamines and gastric acidity have been suggested as factors that have an important role in pancreatic cancer, and tooth loss that occurs through poor dental hygiene may be a marker for more deleterious gastrointestinal flora and, consequently, greater endogenous nitrosation. In fact, endogenous formation of nitrosamines in the oral cavity in

individuals with poor oral hygiene is due to elevated levels of nitrate-reducing oral bacteria, including *H. pylori*. The association between *H. pylori* infection and pancreatic cancer was investigated, but this association could not be confirmed.

A recent study has also suggested positive association between periodontitis and pancreatic cancer risk. Myeloperoxidase and superoxide dismutase help to regulate inflammation and are found to be elevated in periodontitis, and polymorphisms of these genes have been associated with elevated pancreatic cancer risk.

## 10. Methods

### 10.1 Patients

Pancreatic tissue specimens were obtained from patients undergoing surgery for ANP (40) and for PC (20) at the Surgical Clinic of the Medical Center of Serbia. The research protocol received institutional evaluation and approval (Ethical Committee of the School of Dentistry, Belgrade). Periodontal evaluation was performed in the hospital, a day before planned surgical procedures, and included assessment of pocket depth (PD in mm) and clinical attachment loss (CAL in mm) at six points of every present tooth (mesio-buccal, mid-buccal, disto-buccal, mesio-lingual, mid-lingual, disto-lingual). The clinical parameters were evaluated with a periodontal probe (XP 23/UNC-15). All measurements were performed by a single periodontist (A.P.). Chronic periodontitis was defined by the presence of at least 4 non-adjacent teeth with sites  $CAL \geq 4mm$  and  $PD \geq 5mm$  (Okuda et al., 2001). All patients that had been taking antibiotics in the previous three months and/or received periodontal treatment were excluded.

12 pancreas specimens obtained during autopsies performed at the Institute of Pathology, School of Medicine, University of Belgrade were also included in the study and used as controls. The cause of death was not related to pancreas.

Immediately after being taken, the specimens were frozen at  $-20^{\circ}C$  until further processing.

### 10.2 Bacterial DNA detection by PCR

Tissue specimens were treated with proteinase K at  $56^{\circ}C$  for 30 minutes, followed by 10 minutes of proteinase K inactivation at  $95^{\circ}C$  and 5 minutes centrifugation in a microfuge to pellet cell debris.

The PCR was performed in volumes of 25  $\mu l$  containing PCR/Mg<sup>++</sup> buffer, 0.2 mM of each dNTP, 0.2  $\mu M$  of each primer, 0.5 U *Taq* DNA polymerase and 3-5  $\mu l$  of template DNA containing supernatant.

The amplification was performed in a DNA Thermal Cycler (Hybaid) programmed at  $94^{\circ}C$  (5 minutes) followed by 35 cycles at  $94^{\circ}C$  (1 min), annealing temperatures adequate for each primer pair (1 min) and extension at  $72^{\circ}C$  (1 minute 30 seconds) plus a final extension at  $72^{\circ}C$  (5 min). The PCR amplified fragments were visualized in an 8% polyacrylamide gel stained with ethidium bromide, on an ultraviolet transilluminator.

Periodontopathogens were detected by means of primer specific PCR. The list of primers, the annealing temperatures as well as the length of the products are given in Table 1. *P. gingivalis* and *A. actinomycetemcomitans* were amplified in the same multiplex PCR reaction, whilst *T. Forshytia* and *P. Intermedia* were coamplified in another multiplex reaction. *E.*

*corrodens* was amplified separately. Specimens of subgingival dental plaque, positive for those microorganisms were used as positive controls. For the negative control, DNA sample was omitted and replaced by water.

Bacteria	Primer pairs	Annealing. t (C°)	Amplicon Size
<i>Porphyromonas gingivalis</i>	AGA GTT TGA TCC TGG CTC AG CAA TAC TCG TAT CGC CCG TTA TTC	55	460 bp
<i>Aggregatibacter actinomycetemcomitans</i>	AGA GTT TGA TCC TGG CTC AG CAC TTA AAG GTC CGC CTA CGT GC	55	600 bp
<i>Tannerella forsythia</i>	AGA GTT TGA TCC TGG CTC AG GTA GAG CTT ACA CTA TAT CGC AAA CTC CTA	53	840 bp
<i>Prevotella intermedia</i>	AGA GTT TGA TCC TGG CTC AG GTT GCG TGC ACT CAA GTC CGC C	53	660 bp
<i>Eikenella corrodens</i>	CTA ATA CCG CAT ACG TCC TAA G CTA CTA AGC AAT CAA GTT GCC C	53	800 bp

Table 1. Primer sequences, annealing temperatures and size of obtained PCR products used for the detection of tested bacteria

11. Results

All 60 patients included in the study were diagnosed as chronic generalized periodontitis with a mean value of PD 3.12±0.35mm and CAL 2.79±0.82mm. A total of 72 specimens have been tested for the presence of 5 different periodontopathogens. The result was considered to be positive if a band of expected size was present on the gel. There was no attempt of sequencing the PCR products or quantifying the infectious agents by real-time PCR. 7 out of 40 specimens of acute necrotizing pancreatitis were positive for the presence of: *E. corrodens* (3 cases), *A. actinomycetemcomitans* (1 case), *P. intermedia* (1 case), *T. forsythia* (3 cases, Fig. 9), and *T. forsythia* and *P. intermedia* simultaneously (1 case). In one specimen of pancreatic cancer *P. intermedia* could be detected. Interestingly, two control specimens obtained from cadavers (cause of death was liver cirrhosis) harbored oral microorganisms.



Fig. 9. Polyacrylamide gel electrophoresis showing bands that represent the product of PCR amplification corresponding to *Tannerella forsythia*



Data on tissue specimen origin and PCR findings are summarized in Table 2.

Tissue	no	<i>Pg</i>	<i>Aa</i>	<i>Pi</i>	<i>Tf</i>	<i>Ec</i>
ANP	40		1	2	2	3
PC	20			1		
NP	12			1	1	

Table 2. The presence of periodontal pathogens in pancreatic tissue. ANP - acute necrotizing pancreatitis, PC - pancreatic cancer, NP - normal pancreatic tissue obtained post-mortem, *Pg* – *Porphyromonas ginivalis*, *Aa* – *Aggregatibacter actinomycetemcomitans*, *Pi* – *Prevotella intermedia*, *Tf* - *Tannerella forsythia*, *Ec* – *Eikenella corrodens*

12. Conclusion

To the best of our knowledge, this is the first time that *E. corrodens*, *A. actinomycetemcomitans*, *P. intermedia* and *B. forsythia* have been described in ANP. Even though it is for some time obvious that periodontal pathogens can enter the circulation, causing transient bacteraemia, there were no systematic assessments of potential association between oral bacteria and extraoral infections. Although *Eikenella* species, for instance, have been shown to cause endocarditis and intraabdominal infection, they are considered a very rare etiological agent (Danzinger et al., 1994; Watkin et al., 2002). Interestingly, we found *E. corrodens* in three cases of acute necrotizing pancreatitis. Four other cases of ANP harbored other periodontal pathogens.

Bacterial infections are usual complications in patients with acute pancreatitis but they typically include *Salmonella*, *Campylobacter*, *Escherichia coli*, *Pseudomonas aeruginosa* etc (Garg et al., 2001; Reimund et al., 2008). Generally, acute pancreatitis is not the primary manifestation of these infections. The presence of dental plaque bacteria in our cases of ANP does not exclude the simultaneous occurrence of other pathogens.

Bacterial translocation which can be defined as the passage of intestinal microbes through the mucosa to internal organs is doubtlessly an important cause of pancreas infection. Nonetheless, other infection routes and infection sources should be considered as well, and the presence of periodontal microorganisms in ANP substantiates the hypothesis of alternative paths. Multiple risk factors of bacterial spreading, including surgery, tumour metastasis in the abdomen, compromising local anatomy and circulation, etc., are known to exist. Presumably, from abdominal aorta, where they can be found, oral bacteria are capable of reaching the main arteries supplying pancreas. Their presence in pancreatic tissue could be tentatively explained by compromised local circulation. The finding of bactDNA in two control pancreatic specimens, in which the cause of death was a non-pancreatic disease (cirrhosis), may be due to some contamination during autopsy. Infections in patients with cirrhosis are frequent and varied and their spreading in the peritoneum cannot be ruled out (Frances et al., 2008). In the present study, liver tissue has not been tested for the presence of periodontopathogens.

The finding of only one case positive for *P. intermedia* in the pancreatic cancer group does not support the concept of direct oral bacteria involvement in the pathogenic processes, in

the same way as seen in atherosclerosis. On the other hand, pancreatic cancer has been previously related to different bacterial infections. Namely, *Helicobacter* DNA was detected in a very high percentage of pancreatic tumors and surrounding tissue (Nilson et al., 2006; Stolzenberg et al., 2001). As *Helicobacter pylori* is also frequently encountered in the oral cavity of individuals with periodontal disease (Souto et al., 2008, Zarić et al., 2009), its occurrence in the present cases of pancreatic cancer is very probable. A rising body of evidence supports the view on microbially induced and inflammation-driven malignancies (Engels et al., 2008; Lochhead&El-Omar, 2008; Michaud, 2007).

Two large cohort studies looked at a link between pancreatic cancer and history of periodontal disease and found a significant association between the two (Michaud et al., 2007, 2008). According to the authors periodontal disease might be a marker of a susceptible immune system or might directly affect cancer risk. Hujoel found a significant association between pancreatic cancer and periodontitis measured by examination but again had a relatively small number of cases within their cohort. The results published by Michaud on increased incidence of pancreatic cancer among patients with periodontal disease could suggest a possible involvement of periodontopathogens in pancreatic cancer. Our study does not really confirm it, or at least does not point to direct, local contribution of oral microorganisms to the pathogenic process. Their role may be considered in terms of infection and chronic inflammation with systemic effect.

The presence of periodontopathogens in various arteries, however, is an important finding. It means that oral microorganisms have theoretically the possibility to migrate to organs distant from their primary reservoir-the oral cavity, and invade them. Whether it will result in clinical or subclinical pathological changes remains uncertain.

In periodontitis, periodontal pathogens and their products, as well as inflammatory mediators produced in periodontal tissues, might enter the bloodstream and contribute to the global inflammatory burden, causing systemic effects and/or contributing to systemic diseases. Several bacteria can promote or initiate abnormal cell growth by evading the immune system or suppressing apoptosis. Since periodontitis is a chronic oral bacterial infection, few authors have suggested a possible positive association between periodontitis and pancreatic cancer. To our knowledge, this is the first study which demonstrated the presence of periodontal bacteria in pancreatic tissue. Relatively low percentage of positive findings in our study does not represent a reliable proof of a link between periodontopathogens and pancreatic diseases. This might be explained by the fact that destruction of periodontal tissues in our study group was not extensive. Further researches to confirm association between periodontitis and pancreatic diseases are required.

Epidemiological research (cross-sectional and longitudinal studies) can identify relationships but not causation. If some types of periodontal disease merely constitute an oral component of a systemic disorder or have etiological features in common with systemic diseases, periodontal and systemic diseases might frequently occur together without having a cause effect relationship (Slots, 1998). Medical community should be aware of the potential negative effects of periodontal infections on systemic health. First of all, periodontal infections must be recognized and treated, and then a regular oral care must be maintained. Nevertheless, with information accessible at the moment, it seems justified to state that good oral health is important to maintain good general health.

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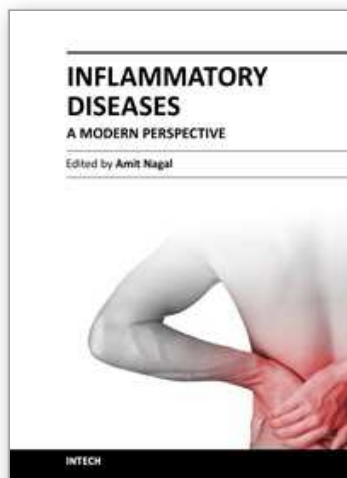
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