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# The Emerging Concepts on the Impact of Periodontitis on Systemic Health

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## 1. Introduction

*Look to thy mouth; diseases enter here - George Herbert (1593-1632)*

Oral health is an integral component of general health and well-being of an individual. Knowledge about the link between periodontal disease and systemic health is growing rapidly. Increasing evidence is available indicating periodontitis as a risk factor for various systemic diseases such as cardiovascular diseases, diabetes mellitus, low birth weight infants and pulmonary diseases (Cullinan et al., 2009; Scannapieco et al., 2010). To date, the bulk of evidence points to the higher levels of circulating periodontal bacterial components, such as endotoxins, that could travel via blood to other organs in the body and cause harm (Dave and Van Dyke, 2008). The relationship between periodontal bacteria and systemic diseases was investigated extensively during the past two decades. More recently, a wealth of epidemiological, clinical and laboratory studies have provided irrefutable evidence that periodontal disease negatively impacts systemic health and proposed mechanisms by which such an association may occur (Fisher et al., 2008; Marakoglu et al., 2008). It is now widely accepted that periodontitis can induce pro-inflammatory cytokines, chemokines and mediators which may play a major role in the development of a variety of systemic conditions (Kuo et al., 2008). However, with the knowledge of possible links between periodontal disease and systemic conditions, patients with advanced periodontitis could be considered systemically compromised even in the absence of overt clinical symptoms or illness.

As science discovers new ways to identify the specific disease process and pathogens, the dental profession discovers new ways to manage the disease from a medical approach. This chapter is focused on evaluating and updating the current status of oral infections, especially periodontitis, as a causal factor for systemic diseases, such as cardiovascular diseases, diabetes mellitus, respiratory disorders, preterm low birth weight and osteoporosis.

## 2. Periodontal etiopathogenesis

The pathogenesis of human periodontitis was placed on a rational footing for the first time by Page and Schroeder (1976). The destructive process is initiated by the bacterial lipopolysaccharides (LPS) but propagated by the host. Microorganisms such as *Porphyromonas gingivalis, Tannerella forsythia (*formerly *Bacteroides forsythus),* and *Aggregatibacter actinomycetemcomitans* (formerly *Actinobacillus actinomycetemcomitans)* produce enzymes that breakdown the extra cellular matrix such as collagen and host cell membrane to produce nutrients for their growth and further tissue invasion, thereby, initiating an immune and inflammatory process which stimulates the host to release various pro-inflammatory cytokines, MMPs, prostaglandins and host enzymes. They break up the collagen and tissues, creating inroads for further leukocytic infiltration. As periodontal disease progresses, collagen fibres and connective tissue attachment to the tooth are destroyed and epithelial cells proliferate apically deepening the periodontal pockets. This leads to migration of junctional epithelium apically, thereby, exposing the alveolar bone resulting in the activation of osteoclasts initiating bone destruction.

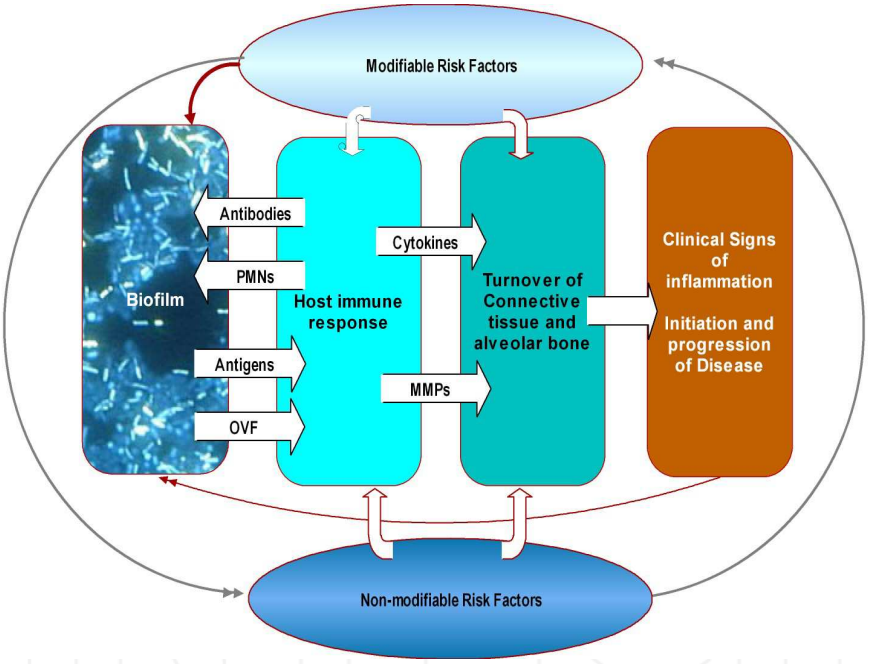


Fig 1. Pathogenesis of Periodontitis – the interplay of modifiable and non-modifiable risk factors (LPS - Lipopolysaccharide, OVF-Other virulence factors, MMP-Matrix metalloproteinases, PMN-Polymorphonuclear leukocytes).

## 3. Focal infection: The changing concepts

The theory of focal infection, which was promulgated during the 19th and early 20th centuries, stated that "foci" of sepsis were responsible for the initiation and progression of a variety of

inflammatory diseases such as arthritis, peptic ulcers and appendicitis (Scannapieco, 1998). Therapeutic edentulation or the "clean-sweep" was common as a result of the popularity of the focal infection theory. Since many teeth were extracted without evidence of infection, thereby providing no relief of symptoms, the theory was discredited and largely ignored for many years (Dussault and Sheiham, 1982). However, 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 immune-compromised hosts such as patients suffering from malignancies, diabetes, rheumatoid arthritis or having corticosteroid and 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 (Li et al., 2000). The anatomic closeness of this oral microflora to the bloodstream can facilitate bacteremia and systemic spread of bacterial products, components and immune complexes.

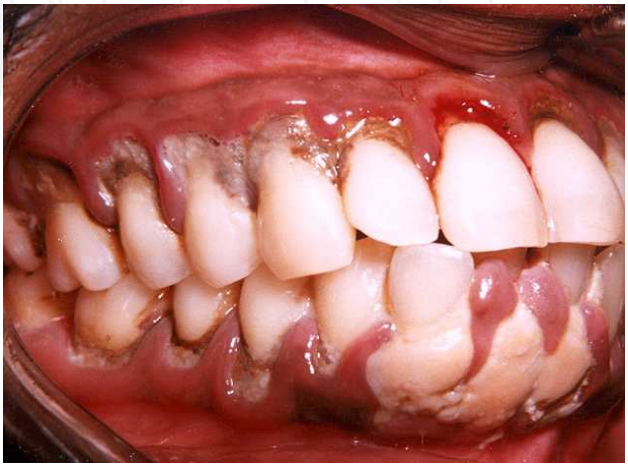

Fig. 2. A case of periodontitis showing the inflammatory process and destruction of the supporting tooth structures.

### 3.1 Possible pathways of oral infections and non-oral diseases

| Pathway for oral infection | Possible non oral diseases |
|---|---|
| **Metastatic infection from oral cavity via transient bacteremia** | Subacute infective endocarditis, acute bacterial myocarditis, brain abscess, cavernous sinus thrombosis, sinusitis, lung abscess/infection, Ludwig's angina, orbital cellulitis, skin ulcer, osteomyelitis, prosthetic joint infection |
| **Metastatic injury from circulation of oral microbial toxins** | Cerebral infarction, acute myocardial infarction, abnormal pregnancy outcome, persistent pyrexia, idiopathic trigeminal neuralgia, toxic shock syndrome, systemic granulocytic cell defects, chronic meningitis |
| **Metastatic inflammation caused by immunological injury from oral organisms** | Behcet's syndrome, chronic urticaria, uveitis, inflammatory bowel disease, Crohn's disease |

Table 1.

### 3.2 Emergence of periodontal medicine

Most studies concerning the relationship between oral infection and systemic diseases are related to periodontal disease, by far the most common oral infection. The term periodontal disease is used to describe a group of conditions that cause inflammation and destruction of the supporting structures of the teeth. Periodontal disease is caused by bacteria found in the dental plaque and about 10 species have been identified as putative pathogens. *A. actinomycetemcomitans*, *P. gingivalis* and *T. forsythia* are the gram-negative bacteria most commonly associated with periodontitis (Haffajee and Socransky, 1994).

The term Periodontal medicine as suggested by Offenbacher, is defined as a rapidly emerging branch of periodontology focusing on the wealth of new data establishing a strong relationship between periodontal health or disease and systemic health or disease. Logically included in this definition would be new diagnostic and treatment strategies that recognize the relationship between periodontal disease and systemic disease (Williams and Offenbacher, 2000).

Page (1998) 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.**

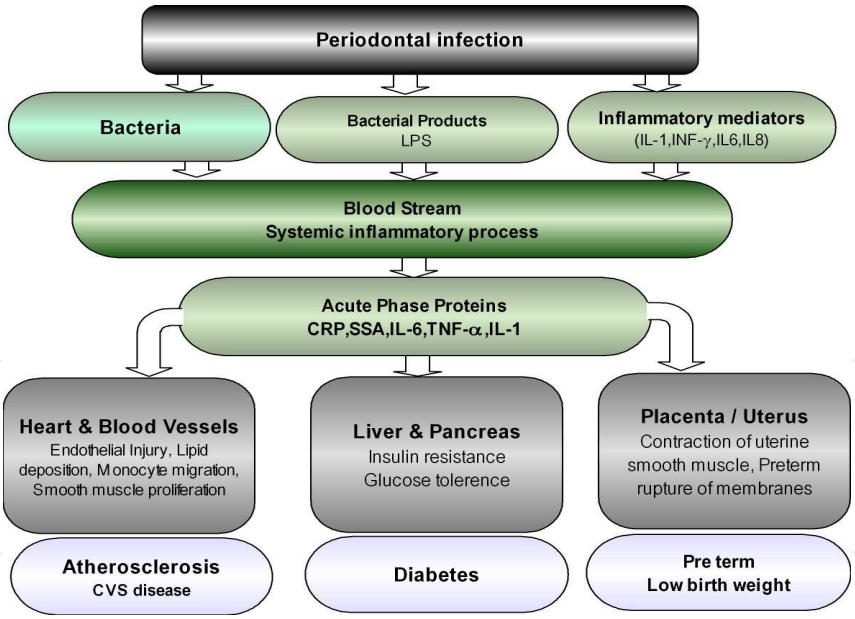


Fig. 3. Periodontal infection and systemic conditions - Potential linkage and possible pathogenic mechanisms (CRP-C-reactive protein, LPS- lipopolysaccharide, IL-1- interleukin-**1**،IL-6 - interleukin-6, IL-8 - interleukin-8, SSA – Sjogrens's antibodies , INF-γ-Interferon-gamma, TNF-α Tumor necrosis factor-alpha ).

### 3.2.1 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 disease (cardiovascular disease) are tobacco smoking, stress, aging, race or ethnicity and male gender (Page, 1998).

### 3.2.2 Subgingival biofilms

Presence of subgingival biofilms constitutes an enormous and constant bacterial load. They present continually renewing reservoir 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, intravascular coagulation, vascular smooth muscle proliferation and fatty degeneration. (Mattila, 1989; Marcus and Hajjar, 1993). LPS upregulates expression of endothelial cell adhesion molecules and secretion of interleukin-1 (IL-1), tumor necrosis factor alpha (TNF-α) and thromboxane, which results in platelet aggregation and adhesion, formation of lipid-laden foam cells and deposition of cholesterol and cholesterol esters.

### 3.2.3 Periodontium as a cytokine reservoir

The pro-inflammatory cytokines TNF-α, IL-1β, and gamma interferon as well as prostaglandin $E_2$ ($PGE_2$) reach high tissue concentrations in periodontitis (Page, 1998). The periodontium can therefore serve as a renewing reservoir for spill-over of these mediators, which can enter the circulation and induce as well as perpetuate systemic effects. IL-1β favors coagulation and thrombosis and retards fibrinolysis (Clinton et al., 1991). These mediators emanating from the diseased periodontium may also account for preterm labor and low-birth-weight infants.

## 4. Periodontitis and cardiovascular system

Cardiovascular diseases such as atherosclerosis and myocardial infarction occur as a result of a complex set of genetic and environmental factors (Herzberg and Weyer, 1998). The genetic factors include age, lipid metabolism, obesity, hypertension, diabetes, increased fibrinogen levels and platelet-specific antigen Zwb ($P1^{A2}$) polymorphism. Environmental risk factors include socioeconomic status, exercise, stress, diet, non- steroidal anti-inflammatory drugs, smoking and chronic infection.

### 4.1 Epidemiology of periodontal disease and cardiovascular disease

According to the National Health and Nutrition Examination Survey (NHANES III) carried out between 1988 and 1994, 34.5% of dentate U.S. citizens 30 years or older had periodontitis. The prevalence of periodontitis increased with increasing age (Albandar et al., 1999) in developed countries. Cardiovascular disease accounts for 50% of deaths (WHO, 1995) and is considered the leading cause of death in the United States (Rosenberg et al., 1996).

### 4.2 Dental plaque to atherosclerotic plaque

Several mechanisms have been proposed to explain how periodontal disease initiated by the microorganisms in the dental plaque can contribute to the development of cardiovascular

diseases. The mechanisms associating plaque microorganisms to periodontal disease are discussed in the following section.

#### 4.2.1 First mechanism

Oral bacteria such as *Streptococcus sanguis*, *P. gingivalis* have collagen like molecule (platelet aggregation associated protein) on their surface (Herzberg et al., 1994) which induces platelet aggregation leading to thrombus formation (Herzberg and Meyer, 1996). When *S. sanguis* is injected intravenously into rabbits, a heart attack-like series of events occur. Antibodies which are reactive to periodontal organisms localize in the heart and trigger complement activation, leading to a series of events causing sensitized T cells and heart disease (Herzberg and Meyer, 1996). Deshpande et al (1998) showed that *P. gingivalis* can actively adhere to and invade fetal bovine heart endothelial cells, bovine aortic endothelial cells and human umbilical vein endothelial cells. Potempa et al(2003) studied proteolytic enzymes referred to as "gingipains R", which when released in large quantities from *P. gingivalis* enter the circulation and activate factorX, prothrombin and protein C, promoting platelet aggregation, finally resulting in intravascular clot formation. *P. gingivalis* and *S. sanguis*, may be isolated from atherosclerotic plaques taken from human carotid endarterectomy specimen (Chiu, 1999; Haraszthy et al., 2000). Putative periodontal pathogens that have been investigated for the development of cardiovascular disease include *Chlamydia pneumoniae, Helicobacter pylori*, Herpes Simplex Virus (HSV), Hepatitis A virus (HAV) and Cytomegalovirus (CMV)

#### 4.2.2 Second mechanism

Patients with certain forms of periodontal disease, such as early-onset periodontitis and refractory periodontitis, possess a hyper inflammatory monocyte phenotype which is an exaggerated host response to a given microbial or LPS challenge. Peripheral blood monocytes from these individuals with the hyper inflammatory monocyte phenotype secrete 3 to 10 fold greater amounts of $PGE_2$, TNF- α, and IL-1β in response to LPS than those from normal monocyte phenotype individuals (Hernichel-Gorbach et al., 1994; Offenbacher et al., 1994).

#### 4.2.3 Third mechanism

LPS from periodontal pathogens transferred to the serum as a result of bacteremia or bacterial invasion may have a direct effect on endothelia thereby promoting atherosclerosis (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-α on vascular endothelium and smooth muscle (Thom et al., 1992; Beck et al., 1996). The increase in fibrinogen and WBC count 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).

#### 4.2.4 Fourth mechanism

An elevated level of C-reactive protein, a non-specific marker of inflammation, has been associated with an increased risk of cardiovascular disease. Periodontitis as an infection may

stimulate the liver to produce C-reactive protein (CRP), which in turn will form deposits on injured blood vessels. CRP binds to cells that are damaged and fixes complement, which activates phagocytes, including neutrophils. These cells release nitric oxide, thereby contributing to atheroma formation (Genco et al., 2002). In a study of 1,043 apparently healthy men, baseline plasma concentrations of CRP predicted the risk of future myocardial infarction and stroke (Ridker et al., 1997). Ebersole et al (1997) found that patients with adult periodontitis had higher levels of CRP and haptoglobin which declined significantly after periodontal therapy when compared to subjects without periodontitis. In a study by Loos et al (2000) among 153 systemically healthy subjects consisting of 108 untreated periodontitis patients and 45 control subjects, it was found that mean plasma CRP levels were higher among periodontitis patients. They also reported that patients with severe periodontitis had significantly higher CRP levels than mild-periodontitis patients, and both had significantly higher levels than the controls. Another study by Genco et al (2001) evaluated the relationship of cardiovascular disease and CRP. Groups of adults who had neither periodontal nor cardiovascular disease, one of these diseases, or both of them were assembled. In those with both heart disease and periodontal disease, the mean level of CRP (8.7 g/ml) was significantly different from that (1.14 g/ml) in controls with neither disease. The study revealed that treatment of the periodontal disease caused a 65% reduction in the level of CRP at 3 months.

#### 4.2.5 Fifth mechanism

A specific heat shock protein, Hsp65, has been reported to link cardiovascular risks and host responses. Heat shock proteins are important for the maintenance of normal cellular function and may have additional roles as virulence factors for many bacterial species (Young and Elliott, 1989). In animal studies, Xu et al (1993) demonstrated that immunization of rabbits with bacterial Hsp65 induces atherosclerotic lesions. Bacterial infection stimulates the host response to Hsp65, which is a major immunodominant antigen of many bacterial species. The interaction between expressed Hsp65 and the immune response induced by bacterial infection is hypothesized to be responsible for the initiation of the early atherosclerotic lesion (Xu et al., 1993). It has been suggested that chronic oral infection stimulates high levels of Hsp65 in subjects with high cardiovascular risk (Loesche and Lopatin, 1998). Thus, if antibodies directed towards bacterial heat shock proteins cross-react with heat shock proteins expressed by the host tissue, especially those found in the lining of blood vessels, then some oral species might well be the link between oral infection and cardiovascular disease (Loesche and Lopatin, 1998).

#### 4.2.6 Sixth mechanism

**MMPs**: MMPs, including the collagenases, likely play an important role in periodontal tissue breakdown (Lee et al., 2004) as well as destabilization of atheromas leading to heart failure and the deleterious changes in extracellular matrix in the myocardium. In fact, there is increasing evidence that inhibition of MMPs, already shown to be effective for inhibition of periodontal attachment loss, can also inhibit the development of cardiac failure (Matsumura et al., 2005).

### 4.3 Common risk factors for periodontal disease and cardiovascular disease

The difficulty in drawing a cause and effect relationship between periodontitis and cardiovascular disease stems from the fact that the two groups of diseases share many risk

factors. Risk factors, such as smoking, genetics, stress and increasing age, could independently lead to periodontal disease and cardiovascular disease.

### 4.3.1 Smoking

Smoking is a significant risk factor for both diseases. Current evidence suggests that an important component of cigarette smoke, aryl hydrocarbons (Singh et al., 2000), have the ability to inhibit bone formation, particularly in the presence of periodontal disease-causing bacterial co-factors (Singh et al., 2000). As such, these data could help to explain, in part, how cigarette smoking might lead to periodontal bone loss. Interestingly, we now also have data to suggest that these same aryl hydrocarbons may promote vascular disease, as measured by vascular calcification (Usman, 2004). Thus, a common risk factor, smoking/aryl hydrocarbons, mitigates negative effects in two disparate systems: the periodontium and vascular tissues.

### 4.3.2 Association between periodontal disease and atherosclerosis

Atherosclerosis has been defined as a progressive disease process that involves the 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 (Boon et al., 1995). The presence of atheroma tends to make the patient thrombosis-prone because the associated surface enhances platelet aggregation and thrombus formation that can occlude the artery or be released to cause thrombosis, coronary heart disease and stroke. A study report indicated that atherosclerotic plaques are commonly infected with gram-negative periodontal pathogens, including *A. actinomycetemcomitans* and *P. gingivalis* (Haraszthy et al., 2000).

## 5. Periodontal disease and diabetes mellitus

Diabetes mellitus represents a group of complex metabolic disorders characterized by hyperglycemia resulting from defects in insulin secretion, insulin action or both resulting in inability of glucose to be transported from blood stream into tissues and a consequent excretion of sugar in the urine (Harmel et al., 2004).

Diabetes occurs in two major forms: **Type 1 diabetes** previously called as **'insulin-dependent diabetes mellitus'** is the result of a reduction in or the elimination of insulin production by beta cells in the pancreas. Reduced insulin production is most often the result of destruction of the beta cells, probably due to autoimmune or viral disease. Individuals with type 1 diabetes require daily insulin supplementation to properly regulate glucose use. Insulin delivery is usually by injection, although progress has been made with the use of insulin pumps and pancreatic transplantation that provides an endogenous source of insulin. **Type 2 diabetes** previously called **'non-insulin-dependent diabetes mellitus'** is characterized by a deficient response to insulin by target cells, although insulin production is typically normal or even enhanced in these individuals. This impairment may be due to changes in the structure or number of the cell receptors for insulin. It is suggested that type 2 diabetes may be a disorder of the innate immune system and results from a chronic, low-level inflammatory process (Pickup and Crook, 1998). This form of diabetes is by far the most common (estimated to be 85%-90% of all diabetes). Although the precise etiology is still uncertain in both types of primary diabetes, environmental factors interact with genetic

susceptibility to determine which of those with the genetic predisposition actually develop the clinical syndrome and the timing of its onset. Environmental factors in insulin-dependent diabetes include virus, diet, immunological factors and pancreatic disease. In non-insulin-dependent diabetes, environmental factors such as lifestyle, age, pregnancy, pancreatic pathology, insulin secretion and resistance are included.

### 5.1 Inter-relationships between periodontal diseases and diabetes mellitus

The interrelationship between diabetes and periodontal disease is established through a number of pathways and is bidirectional. Diabetes is a risk factor for gingivitis and periodontitis. Blood sugar control is an important variable in the relationship between diabetes and periodontal disease. Individuals who have poor glycemic control have a greater prevalence and severity of gingival and periodontal inflammation. It has been suggested that hyperglycemia promotes periodontitis and its progression.

One plausible biologic mechanism for why diabetics have more severe periodontal disease is that glucose-mediated advanced glycation end-products (AGE) accumulation affects the migration and phagocytic activity of mononuclear and polymorphonuclear phagocytic cells, resulting in the establishment of a more pathogenic subgingival flora. The maturation and gradual transformation of the subgingival microflora into an essentially gram-negative flora will in turn constitute, via the ulcerated pocket epithelium, a chronic source of systemic challenge. This in turn triggers both an "infection-mediated" pathway of cytokine upregulation, especially with secretion of TNF-α and IL-1, and a state of insulin resistance, affecting glucose-utilizing pathways. The interaction of mononuclear phagocytes with AGE-modified proteins induces upregulation of cytokine expression and induction of oxidative stress. Thus, monocytes in diabetic individuals may be "primed" by AGE-protein binding. Periodontal infection challenge to these primed phagocytic cells may, in turn, amplify the magnitude of the macrophage response to AGE-protein, enhancing cytokine production and oxidative stress. Simultaneously, periodontal infection may induce a chronic state of insulin resistance, contributing to the cycle of hyperglycemia, nonenzymatic irreversible glycation, AGE-protein binding and accumulation, amplifying the classical pathway of diabetic connective tissue degradation, destruction and proliferation. Hence, the relationship between diabetes mellitus and periodontal disease or infection becomes bi-directional. A self-feeding two-way system of catabolic response and tissue destruction ensues, resulting in more severe periodontal disease and increased difficulty in controlling blood sugar.

Studies on Pima Indians, who have a very high rate of diabetes, show a higher prevalence and incidence of periodontal attachment loss and alveolar bone loss than control populations (Nelson et al., 1990). Both diseases have a relatively high incidence in the general population and are polygenic disorders featuring some degree of immune system dysfunction (Anil et al., 1990a; Anil et al., 1990b). Most of the early studies tended to consider the relationship between the two diseases as unidirectional, with a higher incidence and severity of periodontitis in patients with diabetes. Studies have suggested evidence for a bidirectional adverse interrelationship between diabetes and periodontal diseases (Taylor et al., 2004). In particular, individuals susceptible to diabetes and those with poor metabolic control may experience one or more complications in multiple organs and tissues. The evidence for a bidirectional relationship between the two conditions comes from studies conducted in distinctly different settings worldwide (Taylor, 2001).

A model was presented by Grossi and Genco (1998), in which severe periodontal disease increases the severity of diabetes mellitus and complicates metabolic control. They proposed that an infection-mediated upregulation cycle of cytokine synthesis and secretion by chronic stimulus from LPS and products of periodontopathic organisms may amplify the magnitude of the AGE-mediated cytokine response that is operative in diabetes mellitus. The combination of these two pathways, infection and AGE-mediated cytokine upregulation, helps explain the increase in tissue destruction seen in diabetic periodontitis and how periodontal infection may complicate the severity of diabetes and the degree of metabolic control, resulting in a two-way relationship between diabetes mellitus and periodontal disease or infection. Overall, the evidence supports the view that the relationship between diabetes and periodontal diseases is bidirectional. Further, rigorous systematic studies are warranted to firmly establish that treating periodontal infections can contribute to glycemic management and possibly to a reduction in the complications of DM.

### 5.2 Periodontal treatment and the glycemic control in diabetic patients

It has been made clear that severe periodontitis is associated with poor blood sugar control and that effective periodontal treatment can improve some complications of diabetes, especially hyperglycemia. Periodontal treatment has been shown to improve the metabolic control of diabetic patients, thereby influencing a reduction in glycated and glycemic hemoglobin levels (Faria-Almeida et al., 2006).

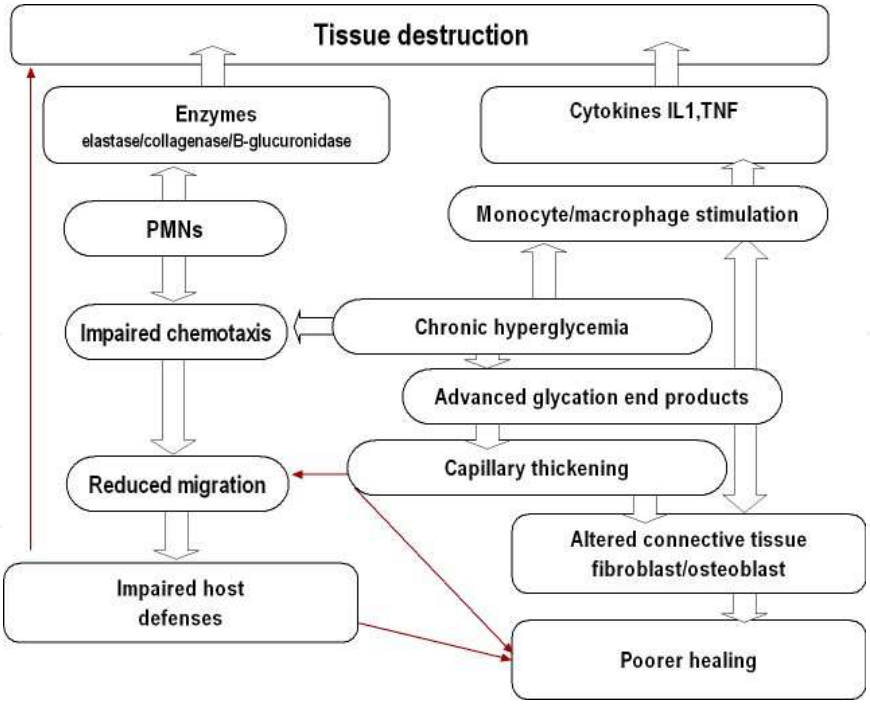


Fig. 4. Effect of diabetes mellitus on host response.

The majority of periodontal treatment studies have shown some improvement in diabetic control as measured by a reduction in $HbA_{1c}$ levels, but some of these studies only had small numbers of patients. A recent meta-analysis of 456 patients has shown that the reductions in $HbA_{1c}$ were small and not statistically significant. Hence, further studies with larger sample sizes and including only type 2 diabetics are needed before definite conclusions can be drawn. Even so, $HbA_{1c}$ levels tend to increase over time in diabetics, and so even a small reduction may be of clinical significance for individual patients, especially as the studies do seem to show a lot of inter-individual variation.

A systematic review of the literature by Grossi et al (1994) concluded that the effect on diabetic status was dependent upon the treatment modality. Studies that investigated the effect of only mechanical debridement were unable to demonstrate any effect on blood glucose level or glycated hemoglobin level regardless of periodontal disease severity or degree of diabetes control. However, all three studies that added systemic antibiotics to mechanical debridement demonstrated improved metabolic control of diabetes. Results from a randomized clinical trial conducted on the Pima population indicated that all subjects that were treated with doxycycline experienced a reduction in glycated hemoglobin. These results suggest that periodontal antimicrobial treatment may reduce the level of glycated hemoglobin in diabetic subjects and may ultimately hold the potential to reduce diabetic sequelae.

There is a strong bidirectional relationship between periodontal diseases and diabetes. Not only are populations and patients with uncontrolled diabetes more susceptible to periodontal diseases, but the presence of active periodontal disease can worsen glycemic control. Effective periodontal therapy combined with systemic antibiotics appears to have a dual effect for diabetic patients, by reducing periodontal infection and improving glycemic status. Dental professionals should also monitor the patient's glycemic control in order to provide optimal dental care.

## 6. Periodontal disease and adverse pregnancy outcomes

There is emerging evidence of a relationship between periodontal health and adverse pregnancy outcomes, particularly preterm birth (PTB)/preterm low-birth-weight infants (PLBW). PTB and low birth weight (LBW) are considered to be the most relevant biological determinants of newborn infants survival, both in developed and in developing countries. The term "adverse pregnancy outcomes" include conditions such as preterm low-birth weight (PLBW) infants, infants born small for gestational age, miscarriage, and pre-eclampsia (Bobetsis et al., 2006). According to the World Health Organization, low birth weight (LBW) is defined as a birth weight <2500g. This low birth weight may be either due to pre-term birth or full term infants who had intra-uterine growth restriction (IUGR) which results in the infant being born small for gestational age (Kramer, 2003). Pre-term births occur mainly because of premature rupture of membranes of preterm labor.

Infection of the chorioamnionic, or extraplacental membrane, may lead to chorioamnionitis, a condition strongly associated with a premature membrane rupture and preterm delivery (Mueller-Heubach et al., 1990). This suggests that distant sites of infection or sepsis may be targeting the placental membranes. PLBW is a major cause of infant mortality and morbidity that poses considerable medical and economic burden on the society (Alves and Ribeiro, 2006). PTB remains a significant public health issue and it is the leading cause of neonatal death and other health problems including neurodevelopmental disturbances (Williams et al., 2000).

Many risk factors have been proposed to cause preterm rupture of membranes and preterm labor. Identified risk factors for PLBW include maternal age; African-American ancestry, low socio-economic status, inadequate prenatal care, drug, alcohol and tobacco abuse; hypertension, genitourinary tract infection, diabetes mellitus (DM), previous PLBW and multiple pregnancies. Smoking during pregnancy has been linked to 20-30% of LBW births and 10% of fetal and infant deaths (Boutigny et al., 2005). Infection is also considered as a major cause of PLBW deliveries, accounting for 30% and 50% of all cases (Offenbacher et al., 1998; Marakoglu et al., 2008).

It has been proposed that one important factor contributing to the continuing prevalence of infants with PLBW is the effect of maternal burden of infection. In this context, periodontal infection may be of importance. Studies have shown that conditions such as bacterial infection of the genitourinary tract, bacterial vaginosis and a high prevalence of maternal lower genitourinary tract infections are associated with adverse pregnancy outcomes. It is also possible that infectious processes occurring elsewhere in the body may contribute to neonatal morbidity and mortality which suggests that periodontal disease may be one such infection.

### 6.1 Pathogenic mechanisms linking periodontal disease to adverse pregnancy outcomes

Evidence suggests a role for inflammation and endothelial activation in the pathophysiology of preeclampsia (Roberts et al., 1989); periodontal infection is one of many potential stimuli for these host responses. The risk for PLBW may be increased by distant infections which result in translocation of bacteria or their components. Distant sites of infection or sepsis such as periodontal disease may target the placental membranes through biological mechanisms involving bacterially induced activation of cell-mediated immunity leading to cytokine production and ensuing synthesis and release of prostaglandin, which can trigger preterm labor (Hillier et al., 1988). Cytokines such as IL-1, IL-6, and TNF-α are all potent inducers of both prostaglandin synthesis and labor and the levels of these cytokines have been found to be elevated in the amniotic fluid of patients in preterm labor with amniotic fluid infection (Romero et al., 2006). Intra-amnionic levels of $PGE_2$ and TNF-α rise steadily throughout pregnancy until a critical threshold is reached to induce labor, cervical dilation, and delivery (Offenbacher et al., 1996). Since these cytokines function as physiological mediators of labor and delivery, any condition that results in an increase in their levels may have the potential of resulting in PTB and LBW. As a remote gram-negative infection, periodontal disease may have the potential to affect pregnancy outcome through these mechanisms. 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-Iβ, TNF-α, IL-6, $PGE_2$ and matrix metalloproteinases (Darveau et al., 1997). During pregnancy, the ratio of anaerobic gram-negative bacterial species to aerobic species increases in dental plaque in the second trimester (Kornman and Loesche, 1980), and this may lead to an increased production of these cytokines. If they escape into the general circulation and cross the placental barrier, they could augment the physiologic levels of $PGE_2$ and TNF-α in the amniotic fluid and induce premature labor. Moreover, it has been demonstrated in a rabbit model that chronic maternal exposure to the periodontal pathogen *P. gingivalis* results in systemic dissemination, transplacental passage, and fetal exposure (Boggess et al., 2005). Studies on murine models have shown that *P. gingivalis* infection during pregnancy results in systemic dissemination of the organism which was associated with IUGR, placenta-specific

translocation of *P. gingivalis*, increased maternal TNF-α and *P. gingivalis*-specific serum IgG levels and a shift in the placental Th1/Th2 cytokine balance (Lin et al., 2003).
Significantly elevated levels of *T. forsythia* and *Campylobacter rectus* among PLBW mothers was reported in a study conducted among African-American and Hispanic subjects (Mitchell-Lewis et al., 2001). These findings suggest that periodontal infection caused by gram negative species which produce LPS may be associated with an increased risk of PLBW. Buduneli et al (2005) compared the periodontal microflora of PLBW mothers and controls in a Turkish population and reported that the bacterial loads of certain species including important periodontal pathogens such as *P. gingivalis, A. actinomycetemcomitams, P. intermedia, and Streptococcus intermedius* were significantly higher among controls than among cases (Buduneli et al., 2005). Although the occurrence rates of *P. intermedia, Fusobacterium nucleatum, Peptostreptococcus micros, C. rectus, Eikenella corrodens, Selenomonas noxia, and S. intermedius* were higher among cases, the differences were not statistically significant. Logistic regression analysis revealed that *P. micros* and *C. rectus* significantly increased the risk of PLBW while *Prevotella nigrescens* and *A. actinomycetemcomitans* decreased the risk.

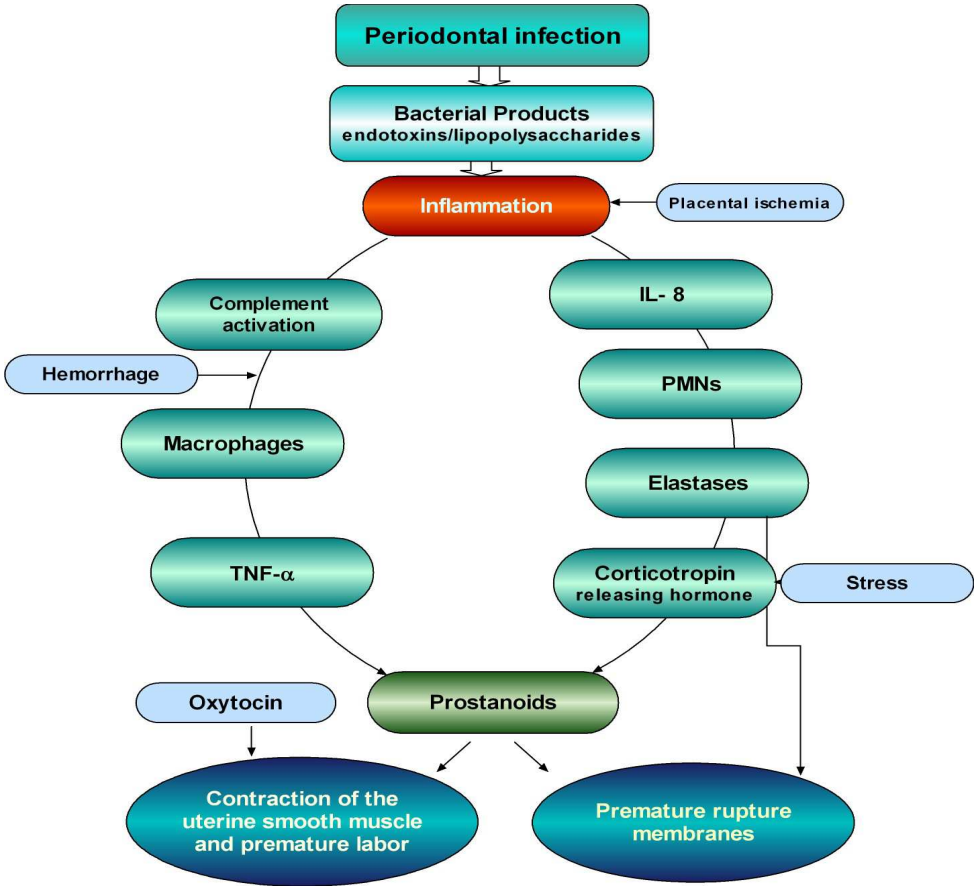


Fig. 5. Proposed biological mechanisms for induction of premature birth.

In a study evaluating the relationship between fetal inflammatory and immune responses to oral pathogens and risk for PTB, umbilical cord blood specimens were examined for presence of fetal immunoglobulin M (IgM) antibody against oral pathogens and levels of C-reactive protein, IL-β, IL-6, TNF-α, $PGE_2$, and 8-isoprostane. The results showed that the presence of IgM antibodies to oral pathogens and increased levels of TNF-α and 8-isoprostane were associated with increased rates of PTB, and that the combined effects of fetal IgM, C-reactive protein, TNF-α, $PGE_2$, and 8-isoprostane resulted in a significantly increased risk for PTB (Boggess et al., 2005). An elevated level of CRP among pregnant patients with periodontitis compared to periodontally healthy subjects has been reported by other investigators (Pitiphat et al., 2006; Horton et al., 2008).
Studies have shown that elevated levels of serum and placental soluble VEGF receptor-1 are associated with an increased risk of pre-eclampsia (Koga et al., 2003; Romero et al., 2008). Elevated levels of soluble VEGF receptors have also been reported in mothers with periodontitis who gave birth to PLBW infants (Sert et al., 2011). Subjects with periodontitis have been shown to have elevated levels of β2-glycoprotein I-dependent anti-cardiolipin autoantibodies; a class of antibodies associated with adverse pregnancy outcomes and fetal loss as well as elevated levels of markers of vascular inflammation (Schenkein et al., 2007).

## 7. Periodontal infection and gastrointestinal diseases

The oral cavity provides a gateway between the external environment and the gastrointestinal tract and facilitates both food ingestion and digestion. Oral hygiene and tooth loss can potentially affect gastrointestinal flora and nutritional status, and thus, they have implications for the development of chronic gastro-intestinal diseases. Poor dental health, tooth loss, or both have been associated with increased risk for chronic gastritis, peptic ulcer and gastrointestinal malignancies, including oral, esophageal and gastric cancers (Abnet et al., 2005; Kossioni and Dontas, 2007).

### 7.1 *Helicobacter pylori* infection

*Helicobacter pylori* (*H. pylori*) is one of the most common bacterial infections of humans (Blaser, 1997). The presence of the organism *H. pylori* (initially termed *Campylobacter pyloridis*) in the antral mucosa of humans was first reported in 1983 (Warren and Marshall, 1983). *H. pylori have* been closely linked to chronic gastritis, peptic ulcer, gastric cancer and mucosa-associated lymphoid tissue (MALT) lymphoma (Dunn et al., 1997; Wang et al., 2002). Although the mode of transmission of *H. pylori* is not yet clear, it has been suggested that oral-oral and fecal-oral routes are the most likely routes (Moreira et al., 2004). The microorganism may be transmitted orally and has been detected in dental plaque and saliva (Krajden et al., 1989; Dowsett et al., 1999). But the role of oral cavity and dental plaque as extra-gastric reservoirs of *H. pylori* is not yet clear. If the oral cavity is an extra-gastric reservoir of the *H. pylori*, it may have a bearing on the treatment of *H. pylori* associated gastric disease on account of the fact that the dental plaque provides protection to the resident microflora (Al Asqah et al., 2009).
Dental plaque has been suggested as a reservoir for *H. pylori(Avcu et al., 2001).*The presence of *H. pylori* has been universally associated with chronic gastritis, and strongly with duodenal ulcer. Previous studies have also identified the microorganism in dental plaque and saliva, which would implicate the oral cavity as a potential reservoir for *H. pylori* or as a possible route of transmission to other sites. Presently, it is not clear whether the oral cavity

permanently harbors viable *H. pylori* or merely serves as the route of transmission to other sites (Kim et al., 2000). In a survey of Dye et al (2002) periodontal disease, specifically periodontal pocket depth, was associated with seroprevalence of *H. pylori.* Furthermore, gastric carriage of *H. pylori* is a known risk factor for gastric cancer, with the cytotoxin-associated gene-A-positive (CagA+) strain having a greater propensity for inflammation, ulceration and malignancy (Stolzenberg-Solomon et al., 2003). The question as to whether the oral cavities, in general, and dental plaque, specifically, are reservoir of *H. pylori,* has been controversial. Desai et al (1991) suggested dental plaque as a permanent reservoir of *H. pylori.* Other investigators, however, would argue against the notion that the oral cavity and dental plaque are permanent reservoirs for *H.* pylori (Kamat et al., 1998). The detection of *H. pylori* by polymerase chain reaction in dental plaque, however, would indicate that the oral cavity may act as a reservoir or sanctuary for the organism (Oshowo et al., 1998).

### 7.2 *H. pylori* and periodontal disease

Among the various studies that have evaluated the relationship between periodontal disease and *H. pylori* infection, some have reported a positive association between the two conditions, while findings from other studies did not support this association. A large scale epidemiological study to evaluate the relationship between *H. pylori* infection and abnormal periodontal conditions was conducted by Dye et al (2002) utilizing the data from the first phase of the third National Health and Nutrition Examination Survey. The authors reported that this association is comparable to the studies on independent effects of poverty on *H. pylori* and concluded that poor periodontal health, characterized by advanced periodontal pockets, may be associated with *H. pylori* infection in adults, independent of poverty status.

### 7.3 *H. pylori* eradication therapy and oral *H. pylori*

Studies have shown that chemotherapy usually employed for the management of *H. pylori*-associated gastric disease, although is successful in eradication of the organism from the gastric mucosa, seldom has any effect on the organism in the dental plaque. In a study in which *H. pylori* was detected in dental plaque and in gastric antral and body mucosa in 98%, 67% and 70%, respectively, of 43 consecutive patients with dyspepsia, triple drug therapy was administered for 15 days to 24 patients. *H. pylori* was eliminated from the gastric mucosa in all 24 patients but persisted in dental plaque in all of them indicating that dental plaque is unaffected by triple drug therapy. Miyabayashi et al (2000) analyzed the correlation between the success of gastric eradication and the prevalence of *H. pylori* in the oral cavity in 47 patients with *H. pylori*-gastritis. Presence of *H. pylori* was determined by nested polymerase chain reaction (PCR) before and after eradication therapy. Of the 24 patients who tested negative for oral *H. pylori* before eradication therapy, *H. pylori* were completely eradicated from the stomach in 22 (92%). None of these patients experienced recurrence during the mean follow-up period of 19.7 months (range 1-48 months). In contrast, 4 weeks after initial therapy, complete eradication of gastric *H. pylori* was achieved for only 12 (52%) of the 23 patients who tested positive for oral *H. pylori*. Of these 12 cases, 7 remained oral positive and 5 became oral negative and 2 of the oral positive cases relapsed within 2 years of initial therapy. Among the 23 patients, oral *H. pylori* were eradicated by therapy only in 8 cases (35%) and one of these relapsed within 2 years of initial therapy. The prevalence of *H. pylori* colonization in dental plaque and tongue scrapings of patients with chronic gastritis and the effect of systemic treatment upon this colonization and eradication

of *H. pylori* from gastric mucosa were studied by Ozdemir et al (2001). Among the 81 patients examined for the study, chronic gastritis was diagnosed in 63 (77.7%) of 81 patients while dental plaque samples of 64 (79%) patients and tongue scraping samples of 48 (59.2%) patients were urease positive. Of the 63 patients with chronic gastritis, dental plaque and tongue scrapings were urease positive in 52 (83%) and 37 (59%) patients, respectively. After 14 days of triple drug therapy (omeprazole, clarithromycin, and amoxicillin), *H. pylori* was eradicated from the gastric mucosa of almost all of the patients, whereas no changes were detected in dental plaque and tongue scrapings by CLO test examination.

### 7.4 Effects of periodontal therapy on the management of *H. pylori*-associated gastric disease

If the hypothesis that oral cavity, dental plaque in particular, is a reservoir for *H. pylori*, then plaque control or periodontal therapy may hold potential benefits in the management of *H. pylori*-associated gastric disease. Very few studies have evaluated the benefits of periodontal therapy in the management of *H. pylori*-associated gastric disease. However, studies conducted in this regard have shown encouraging results. Recently it was reported that plaque control results in lesser prevalence of *H. pylori* in the gastric mucosa (Jia et al., 2009). Another study reported that 77.3% of the patients treated using a combination of periodontal treatment and triple therapy exhibited successful eradication of gastric *H. pylori*, compared with 47.6% who underwent only triple therapy (Zaric et al., 2009).

## 8. Periodontal disease and respiratory disease

The anatomical continuity between the lungs and the oral cavity makes the latter a potential reservoir of respiratory pathogens. The micro-organisms may enter the lung by inhalation, but the most common route of infection is aspiration of what pneumologists have long referred to as oropharyngeal secretions. Therefore, it is plausible that oral micro-organisms might infect the respiratory tract. However, only recently has the role of the oral flora in the pathogenesis of respiratory infection been examined closely (Mojon, 2002).

Current evidence suggests that periodontal disease may be associated with systemic diseases. Respiratory diseases is the term for diseases of the respiratory system, including lung, pleural cavity, bronchial tubes, trachea and upper respiratory tract. They range from a common cold to life threatening conditions such as bacterial pneumonia or chronic obstructive pulmonary disease (COPD), which are important causes of death worldwide (Weidlich et al., 2008). COPD is currently the fourth leading cause of death in the world and further increase in the prevalence and mortality of the disease can be predicted in the coming decades (Pauwels et al., 2001). Chronic bronchitis and emphysema are the most common forms of COPD.

**COPD** is a pathological and chronic obstruction of airflow through the airways or out of the lungs, and includes chronic bronchitis and emphysema. Its main risk factor is smoking, but air pollution and genetic factors are also strongly implicated. *Chronic bronchitis is an inflammatory condition associated with excessive mucus production sufficient to cause cough with expectoration for at least 3 months of the year for 2 or 3 years. Emphysema is the destruction of the air spaces distal to terminal bronchioles.*

**Pneumonia** (both community-acquired and hospital acquired) is an acute infection of the lung and is characterized by cough, breath shortness, sputum production and chest pain. It is caused by the micro-aspiration of oropharyngeal secretions containing bacteria into the lung, and failure of the host to clear the bacteria (Weidlich et al., 2008).

### 8.1 Relationship between periodontal infection and respiratory disease

There is increasing evidence that a poor oral health can predispose to respiratory diseases, especially in high-risk patients. The oral cavity is contiguous with the trachea and may be a portal for respiratory pathogen colonization. Dental plaque can be colonized by respiratory pathogens (Didilescu et al., 2005) which may be aspirated from the oropharynx into the upper airway and then reach the lower airway and adhere to bronchial or alveolar epithelium (Scannapieco, 1999). A systematic review done by Azarpazhooh and Leake (2006) concluded that there is fair evidence of an association of pneumonia with oral health, but there is poor evidence of a weak association between COPD and oral health. A prospective study conducted with 697 elderly individuals observed that the adjusted mortality due to pneumonia was 3.9 times higher in subjects with periodontal disease (Awano et al., 2008). Scannapieco *et al* (2003) conducted a systematic review about the effectiveness of oral decontamination to prevent pneumonia. An association between poor oral health and chronic obstructive pulmonary disease (COPD) was observed on analysis of existing large databases such as the Veterans Administration Normative Aging Study and the National Health and Nutrition Examination Survey III (NHANES III), after controlling for confounding variables such as smoking, sex, age and socioeconomic status(Scannapieco and Ho, 2001). Awano et al (2008) conducted a study which concluded that an increase in teeth with periodontal pockets in the elderly may be associated with increased mortality from pneumonia. A systematic review of 21 studies reports on the impact of periodontal disease and other indicators of poor oral health on the initiation or progression of pneumonia (Scannapieco et al., 2003).

### 8.2 Mechanism of infection

Several biological mechanisms are hypothesized to explain the link between poor oral health and pneumonia. Two routes exist for oral micro-organisms to reach the lower respiratory tract: hematogenous spread and aspiration.

Hematogenous spread of bacteria is an inevitable adverse effect of some dental treatments and may occur even after simple prophylactic procedures. Nonetheless, this route of infection seems rare.

Aspiration: Three mechanisms of infection related to aspiration of material from the upper airway can be envisioned. First, periodontal disease or poor oral hygiene might result in a higher concentration of oral pathogens in the saliva. These pathogens would then be aspirated into the lung, overwhelming the immune defences. Second, under specific conditions, the dental plaque could harbour colonies of pulmonary pathogens and promote their growth. Finally, periodontal pathogens could facilitate the colonization of the upper airways by pulmonary pathogens. Cytokines and enzymes induced from the periodontally inflamed tissues by the oral biofilm may also be transferred into the lungs where they may stimulate local inflammatory process preceding colonization of pathogens and the actual lung infection (Scannapieco et al., 2001). Other possible mechanisms of pulmonary infection are inhalation of airborne pathogens or translocation of bacteria from local infections via bacteremia. The possibility that bacteria in oral biofilms influence respiratory infection suggests that good oral hygiene may prevent the aspiration of large numbers of oral bacteria into the lower airway and thus prevent initiation or progression of respiratory infection in susceptible individuals. Further studies are required to verify the importance of oral conditions in the pathogenesis of lung diseases such as COPD (Teng et al., 2002).

### 8.3 Microbiological similarities between organisms infecting the lungs and oral flora

The vast majority of pulmonary diseases are due to aerobic bacteria that are found in the oral flora but are not related to any oral diseases. In contrast, the list of anaerobes that are implicated in the destruction of periodontal tissues and that have also been isolated from infected lungs is quite long. For example, *Actinobacillus actinomycetemcomitans* and *Fusobacterium nucleatum* have both been isolated from infected lungs, whereas *Pseudomonas aeruginosa*, a known pulmonary pathogen, has been isolated from patients with "refractory" periodontitis (Slots et al., 1990). The pulmonary pathogenicity of *P. gingivalis* has been confirmed in an animal model simulating aspiration (Nelson et al., 1986). Common potential respiratory pathogens (PRPs) such as *Streptococcus pneumoniae*, *Mycoplasma pneumoniae*, and *Haemophilus influenza* can colonize the oropharynx and will be aspirated into the lower airways.

## 9. Periodontitis and osteoporosis

Osteoporosis is a skeletal disorder characterized by low bone mass and micro-architectural deterioration with a resulting increase in bone fragility and susceptibility to fracture (Cummings and Melton, 2002). It is the most common type of metabolic bone disease, characterized by compromised bone strength. Osteoporosis and periodontal diseases have several risk factors in common, such as increased disease prevalence with increased age, negative impacts of smoking on disease development and severity and impaired tissue healing as a result of the disease. Therefore, it would be interesting for dental professionals to examine the relationship between osteoporosis and periodontal diseases.

### 9.1 Inter-relationships and interactions between periodontal diseases and osteoporosis

Several potential mechanisms have been proposed to explain the association between osteoporosis and periodontal diseases. First, osteoporosis results in loss of BMD throughout the body, including the maxilla and the mandible. The resulting low density in the jawbones leads to increased alveolar porosity, altered trabecular pattern and more rapid alveolar bone resorption following invasion by periodontal pathogens. Second, systemic factors affecting bone remodeling may also modify the local tissue response to periodontal infection, such as increased systemic release of IL-1 and IL-6.

The majority of the literature has investigated the role of osteoporosis in the onset and progression of periodontitis and tooth loss (Weyant et al., 1999; Tezal et al., 2000; Lundstrom et al., 2001). However, chronic infection around multiple teeth could contribute significantly to elevations in circulating IL-6 levels, a predictor of bone loss (Scheidt-Nave et al., 2001). In an animal study, elevated levels of IL-6 were found in the serum and gingival tissues adjacent to deep periodontal pockets (Johnson et al., 1997). Therefore, it is at least theoretically possible that chronic periodontitis may contribute to the development or progression of osteoporosis. Whether individuals with oral osteopenia are at risk for systemic osteopenia and osteoporosis remains to be determined. Medications used for the treatment and prevention of osteoporosis have the potential to reduce alveolar bone loss (Persson et al., 2002; Yoshihara et al., 2004). It has been shown that estrogen used in hormone replacement therapy of postmenopausal women is associated with reduced gingival inflammation and a reduced frequency of gingival attachment loss in osteoporotic women in early menopause (Krall, 2001). The use of bisphosphonate alendronate, an

antiresorptive drug has been shown to lower the risk of bone loss in adults with periodontal disease (El-Shinnawi and El-Tantawy, 2003). There is a possible relationship between osteoporosis and periodontitis which need further investigations.

### 9.2 Effects of periodontal infection on systemic bone loss

Although periodontal diseases have historically been deemed to be the result of an infectious process, others have suggested that periodontal diseases may be an early manifestation of osteoporosis (Whalen and Krook, 1996). The link between these two diseases may be the bone-resorptive process. Increased local production of cytokines associated with periodontal diseases could accelerate systemic bone resorption by modulating the host response. Pro-inflammatory cytokine IL-6, produced by osteoblasts, may play a pivotal role in this potential mechanism. In normal bone homeostasis, IL-6 production stimulates osteoclastic activity resulting in bone resorption. Many of the effects on BMD may also be modulated through IL-6 (Reddy, 2001).

Genetic factors that predispose an individual to systemic bone loss may also predispose them to periodontal destruction. Among several factors that down regulate IL-6 gene expression are estrogen and testosterone. After menopause, IL-6 levels are elevated, even in the absence of infection, trauma or stress. The increased gene expression of IL-6 with age may be the reason why both osteoporosis and chronic periodontal diseases are age related (Ershler and Keller, 2000). Certain lifestyle factors, such as smoking and low calcium intake, may influence the risk of developing osteoporosis and periodontal diseases (Payne et al., 2000).

A growing body of literature has accumulated to investigate the association between osteoporosis and periodontal diseases. Although significant advances have been made in determining the relationship between periodontal disease and osteoporosis, further studies are needed to clarify this correlation. Compared to other systemic diseases, the research done in elucidating the association is limited, and many researchers have highlighted and stressed in their publications this great need for a better understanding of the relationship. Another issue is that periodontal disease is diagnosed largely in males whereas osteoporosis is a disorder predominantly diagnosed in females.

Most published studies explaining the relationship between osteoporosis and periodontal diseases support a positive association between these two common diseases. However, the conclusions drawn from these studies need to be interpreted with caution due to the limitations of the study design, small sample sizes and inadequate control of other confounding factors. Additional well-controlled, large-scale, prospective studies are needed to clarify the situation and to provide a better understanding of the mechanisms by which osteoporosis and periodontal diseases are associated.

## 10. Rheumatoid arthritis and periodontitis

Rheumatoid arthritis (RA) is an autoimmune disease that affects several organs and systems and it is also associated with destruction of joint connective tissue and bone. It has been reported that the patterns of hard and soft tissue destruction in RA is similar to that seen in chronic periodontitis. Besides the similarity in tissue destruction, the two conditions also share certain pathogenic mechanisms such as release of inflammatory mediators which mediate the tissue destruction. This similarity of clinical and pathologic features led to the hypothesis of a bidirectional association between RA and periodontitis which involves RA

affecting the pathogenesis of periodontitis and vice-versa (Mercado et al., 2000; Ribeiro et al., 2005). Both conditions are associated with destruction of bone, mediated by inflammatory cytokines such as interleukin-1, tumor necrosis factor and prostaglandin E2 (Bozkurt et al., 2000). During the inflammatory response, cytokines and matrix metalloproteinases, factors that are essential in the pathogenesis of both diseases, are released from the inflammatory cells (Birkedal-Hansen, 1993; Kjeldsen et al., 1993). An altered function of the inflammatory response and the metabolism of soft and hard tissues may turn out to be identical pathogenic factors (Kornman et al., 1997). A novel cytokine termed Secreted osteoclastogenic factor of activated T cells (SOFAT) has been suggested as factor which may exacerbate inflammation and/or bone turnover under inflammatory conditions such as RA and periodontitis (Rifas and Weitzmann, 2009). An experimental study in which adjuvant arthritis was induced in rats showed that the development of arthritis was associated with an elevation of joint tissue MMPs, TNF-α, and IL-1β compared to control rats. In the gingival tissues of arthritic rat's gelatinase, collagenase, TNF-α and IL-1β were elevated. There was also a significant increase in periodontal bone loss and tooth mobility in arthritic rats (Ramamurthy et al., 2005).

Rheumatoid arthritis also influences the pathogenesis of periodontitis through its motor and emotional impairment (Persson et al., 1999). Motor impairment may make it more difficult to perform adequate oral hygiene. The salivary flow reduction due to medication or secondary Sjogren syndrome may increase supragingival plaque formation in these individuals (Bozkurt et al., 2000). Psychological alterations found among RA patients were suggested as risk indicators for periodontitis (Genco et al., 1999).

Periodontitis might interfere with the pathogenesis of RA through bacteremia, presence of inflammatory mediators, bacterial antigens and immunoglobulins in the serum. It has been demonstrated that RA patients have higher levels of serum antibodies to periodontopathogenic bacteria such as *P. gingivalis, T. forsythia, P. intermedia,* and *Prevotella melaninogenica* (Mikuls et al., 2009). Elevated levels of antibodies to *P. intermedia* and *T. forsythia* have been reported in the synovial fluid samples of RA patients (Moen et al., 2003). Elevated levels of antibodies to *P. gingivalis* have been correlated with RA-related autoantibody and CRP concentrations (Mikuls et al., 2009). Moreover, periodontitis may have systemic repercussions with increased inflammatory mediator levels and frequent transitory bacteremia occurring over a prolonged period of time.

Periodontitis and RA present an imbalance between pro-inflammatory and anti-inflammatory cytokines, which is deemed responsible for the tissue damage. Hence it can be assumed that both these conditions possibly have a common genetic trait (Ribeiro et al., 2005). HLA-DR4 antigens and their subtypes are directly associated with both these diseases (Marotte et al., 2006). The findings of the existing studies on the association between rheumatoid arthritis and periodontitis are conflicting. Sjostrom et al (1989) even described a tendency for better periodontal conditions among rheumatoid arthritis patients. This finding may be explained by a significantly reduced amount of plaque and calculus compared with the control group. Other studies are based on the number of remaining or missing teeth (Malmstrom and Calonius, 1975; Laurell et al., 1989) but, the value of tooth loss as a measure of periodontal infection is questionable. Although a causal relationship between periodontitis and rheumatoid arthritis is not supported by these data, persons with rheumatoid arthritis may, in fact, be more likely to experience advanced periodontitis than non-arthritic persons. Kasser et al (1997) showed that patients with long-standing active rheumatoid arthritis had increased gingival bleeding (50%), greater probing depth (26%),

greater attachment loss (173%), and a higher number of missing teeth (29%) compared with controls. The study controlled for relevant risk factors such as oral hygiene, smoking, male gender and age. Mercado et al (2001) showed that rheumatoid arthritis patients were more than twice as likely to have moderate-to-severe periodontal bone loss and probing depth. The study also showed that rheumatoid arthritis patients with moderate-to-severe periodontitis had more swollen joints. Ishi Ede et al (2008) reported that RA patients had fewer teeth, higher prevalence of sites presenting dental plaque and a higher frequency of sites with advanced attachment loss compared to healthy controls. A self-reported health questionnaire survey combined with an evaluation of oral radiographs in patients referred for periodontal treatment indicated that the prevalence of moderate-to-severe periodontitis was significantly elevated in individuals suffering from rheumatoid arthritis receiving medical treatment of the disease (Mercado et al., 2000). Conversely, individuals referred for periodontal treatment had a higher prevalence of rheumatoid arthritis compared with the general population.

Since periodontitis and rheumatoid arthritis share pathogenic factors at the inflammatory level, it has been suggested that dual purpose therapies which can treat both these conditions may be beneficial in modulating the tissue destructive aspects of the host response. If so, then the latest achievements in treating rheumatoid arthritis with biologic drugs inhibiting proinflammatory cytokines such as TNF and IL-1, also may be beneficial adjuvants in the treatment of periodontitis (Sjostrom et al., 1989). In a study among 40 patients with RA and periodontitis, it was observed that patients receiving non-surgical periodontal therapy demonstrated a significant reduction in RA disease activity score and erythrocyte sedimentation rate compared to patients not receiving periodontal therapy (Ortiz et al., 2009). In the same study, it was also observed that in the 20 patients receiving anti-TNF-α therapy, there was a significant improvement in clinical attachment level, probing depth, bleeding on probing and gingival index scores. Conversely, in another study, it was reported that, in patients with RA and periodontitis, although non-surgical periodontal therapy resulted in reduction of ESR, CRP, and α-1 acid glycoprotein, the reductions were not statistically significant. However, in another group in the same study comprising of periodontitis patients who did not have RA, non-surgical periodontal therapy resulted in improvement of periodontal parameters with associated significant improvements in ESR, CRP, and α-1 acid glycoprotein levels suggesting that RA is a multi-factorial disease (Pinho Mde et al., 2009).

## 11. Periodontitis and cancer

The American Cancer Society estimated 30,990 new oral cancers and 7320 deaths from these cancers in 2006. Dental profession can play a major role in controlling the oral neoplasms. It is estimated that between 65% and 75% of patients with oral cancer initially present to a dentist (Tezal et al., 2007). About 50% of those who are diagnosed will die within 5 years of diagnosis. Because of the well-recognized phenomenon of "field cancerization" in the head and neck region, persons with primary tumours of the oral cavity and pharynx are also more likely to develop cancers of the esophagus, larynx, lung, and stomach. In addition, those with oral cancer often have multiple primary lesions and have up to a 20-fold increased risk of having a second primary oral cancer (Schwartz et al., 1994).

Epidemiological studies have shown a link between periodontal disease and head and neck squamous cell carcinoma. In a case-control study conducted over a period of 6 years to

determine the association between periodontal disease and risk of tongue cancers, it was found that each millimetre of alveolar bone loss was associated with a 5.23-fold increase in the risk of tongue cancer (Tezal et al., 2007). In this study, besides periodontitis, other oral health conditions such as dental caries, tooth loss, restorations, and endodontic treatment were also evaluated and the results showed that periodontitis was the only variable that was significantly associated with oral cancer. Another study by the same investigators revealed that each millimetre of alveolar bone loss was associated with a more than 4-fold increase in the risk of head and neck squamous cell carcinoma (Tezal et al., 2009). In both these studies, the use of alveolar bone loss as a measure of periodontitis was beneficial in establishing the temporal sequence by showing that periodontal disease preceded the diagnosis of cancer.

Data from two multi-centre case control studies conducted in Europe and Latin America also demonstrated that periodontal disease and mouthwash use may be independent risk factors for cancers of head, neck, and oesophagus (Guha et al., 2007). In centres in central Europe, it was found that in subjects with poor oral hygiene, the odds ratio of having oral cancer was 4.51, pharyngeal cancer was 7.66, and laryngeal cancer was 1.95 and cancers of all the 3 sites pooled together was 2.89. Regarding missing teeth, in subjects missing 6-15 teeth, the odds ratio was 0.85, 1.04, 1, and 1.09 for oral cancer, pharyngeal cancer, laryngeal cancer, and for all sites respectively and in subjects missing >15 teeth, there was no significant increase in the risk for cancer. In the centres in Latin America, a similar trend was observed regarding poor oral hygiene. However, the risk for cancer increased with increasing number of missing teeth for subjects missing 6 teeth or more. The authors suggested that the lack of increase in the risk of cancer after loss of more than 15 teeth may be due to the absence of a periodontal pathogen or due to presence of little or no remaining teeth.

Studies have also shown that periodontal disease is also associated with other cancers such as pancreatic, colorectal, prostate, uterine and breast cancers (Michaud et al., 2007; Arora et al., 2010; Soder et al., 2011).

### 11.1 Mechanisms underlying association between periodontal diseases and cancer

Chronic infections such as periodontitis, can play a direct or indirect role in carcinogenesis.

**Role of microorganisms:** Microbial infections have been known to be associated with increased risk for cancer. *H. pylori* infection is a well characterized example of increased cancer risk in the setting of bacterial infection. Periodontitis is a chronic oral infection thought to be caused by gram-negative anaerobic bacteria in the dental biofilm (Loesche and Grossman, 2001). However, recently, the presence of viruses such as human papilloma virus (HPV) (Hormia et al., 2005), cytomegalovirus and Epstein-Barr virus (Saygun et al., 2005), which have been implicated in the etiology of oral cancer, have been reported to be present in dental plaque and periodontal pockets. Inflammation caused by bacterial infection has been shown to increase cancer risk. This has been correlated with aberrant DNA methylation in gastric epithelial cells in the case of *H. pylori* infection. In the periodontal setting with a large variety of microorganisms, bacteria and their products such as endotoxins, enzymes and metabolic by-products which are toxic to surrounding cells may directly induce mutations in tumor suppressor genes and proto-oncogenes or alter signalling pathways that affect cell proliferation and/or survival of epithelial cells.

**Indirect effect through inflammation:** The connection between inflammation and cancer has been suggested as consisting of 2 mechanisms: extrinsic and intrinsic mechanisms. In the extrinsic mechanism, a chronic inflammatory state increases the risk of cancer while in the intrinsic mechanism, acquired genetic alterations trigger tumor development. Chronic infection may stimulate the formation of epithelial-derived tumors through an indirect mechanism involving activation of surrounding inflammatory cells. It may also expose epithelial cells to mutagens. Microorganisms associated with the inflammatory process as well as their products can activate host cells such as inflammatory cells, fibroblasts, and epithelial cells to generate a variety of substances which can induce DNA damage in epithelial cells. Chronic inflammatory processes are frequently associated with the release of large amounts of cytokines, chemokines, growth factors, and other signals that provide an environment for cell survival, proliferation, migration, angiogenesis, and inhibition of apoptosis. This environment may help epithelial cells to accumulate mutations and drive these mutant epithelial cells to proliferate, migrate, and give them a growth advantage (Tezal et al., 2007).

The association between periodontal disease and oral neoplasms is biologically plausible and may be explained by the following mechanisms (Tezal et al., 2007).

- Broken mucosal barrier in the presence of periodontal disease and consequent enhanced penetration of carcinogens such as tobacco and alcohol.
- Increased cellularity in blood vessels and connective tissue in chronic inflammation. Association between chronic inflammation and cancer is coupled with the development of chronic diffuse epithelial hyperplasia which is regarded as a common precursor to intraepithelial neoplasia.
- Immunosupression as a common mechanism leading both to periodontal disease and oral cancer. For example, major concentrations of defensins (which have antibacterial, antiviral, and antitumor activities and are likely to play an important role in killing periodontal pathogens) found in neutrophils and epithelia suggest potential implications for critical immune surveillance within periodontal attachment (Biragyn et al., 2002; Zhang et al., 2002)
- Viruses such as Human Papilloma Virus (HPV) and Herpes Simplex Virus 1 (HSV 1) or *Candida albicans* found both in oral cancer and periodontal disease.
- Bacterial overgrowth in patients with poor oral hygiene may lead to an increased rate of metabolites with possible carcinogenic potential. For example, higher microbial production of carcinogenic acetaldehyde from ethanol has been shown in patients with poor oral hygiene (Homann et al., 2001).
- Shared genetic risk factors: Studies have shown that in dizygotic twins, baseline periodontal disease results in a significant increase in cancer risk while in monozygotic twins, this association was markedly attenuated (Arora et al., 2010).

In summary, substantial evidence supports an association between chronic infections and increased risk of cancer. A specific association between chronic periodontitis and oral cancer is plausible and needs to be explored. Oral cancer is dismissed as benign ulcers, traumatic lesions, or other soft tissue aberrations. Despite the advances in treatment, survival rate from oral cancer has not improved during the last few decades mainly due to advanced stage of oral cancer at the time of diagnosis, remaining around 50%. Thus, identification of high risk populations and early diagnosis appears to be the single most important way to control oral cancer (Tezal et al., 2005).

## 12. Summary

Although periodontal diseases have been traditionally considered as inflammatory diseases of the supporting tissues of the teeth, scientific evidence gathered during the last couple of decades have shown that the detrimental effects of these diseases can affect distant organs and adversely impact the systemic health of periodontitis patients. Moreover, studies have shown that periodontal therapy in patients with systemic diseases may be potentially beneficial in improving the overall health of systemically diseased individuals. Although the relationship of periodontal disease with systemic diseases is still being actively investigated, in the light of currently available evidence, it may be considered prudent to include oral health care programmes in the management of patients with systemic diseases. Thus, the role of dental professionals in the public healthcare system becomes more crucial, and prevention as well as treatment of periodontal diseases should be an important initiative in this respect.

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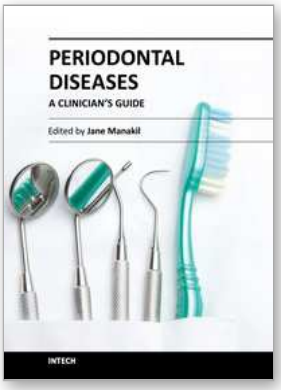


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"Periodontal diseases" is a web-based resource intended to reach the contemporary practitioners as well as educators and students in the field of periodontology. It is fully searchable and designed to enhance the learning experience. Within the book a description is presented of the current concepts presenting the complex interactions of microbial fingerprint, multiple genotypes, and host modulations. In addition, an overview is given of the clinical outcome of the disease's progression, as influenced by the epigenetic factors. Emerging concepts on periodontitis as a risk factor for various systemic diseases and as a bilateral modulating factor have been elucidated in detail as well.

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