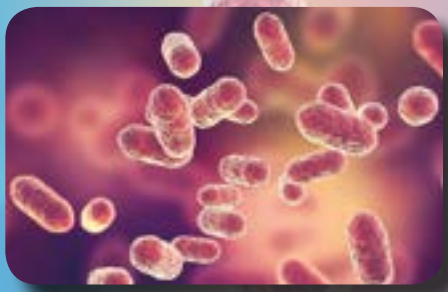
Periodontal Medicine



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Periodontal Medicine

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FOREWORD

I am happy to write a few words about the much needed book on Periodontal Medicine which is a well orchestrated efforts by the author and academician from all over the country. This presentation bears destimoney to the meticulous research by and tiredless effort put in by the authors and their fellow contributors are to be appreciated. I wish the book will all success.

Dr. Sarbesh Prasad Varma
MBBS, MD (Medicine)

ABOUT THE AUTHOR

Dr. Abhishek Verma completed his MDS (Periodontology and Implantology) in 2009 from Sharad Pawar Dental College & Hospital, Wardha, Maharashtra. With the experience of more than 15 years in dentistry. He passed BDS in 2005 from PMNM Dental College & Hospital, Bagalkot, Karnataka. With over 11 years of clinical experience in handling Dental Implants, Periodontal Flap Surgery, Gingival Depigmentation, Ridge Augmentation, Teaching, Training and Monitoring Post Graduate and Under Graduate Student Management; Dr. Verma is presently working as Professor, Dept. of Periodontology & Implantology, Buddha Institute of Dental Sciences and Hospital, Patna, Bihar. He has demonstrated abilities at evaluating monitoring and mentoring student's academic progress; create, innovate and implement career- enhancement programs and activities. Skilled in ensuring teaching design and methods in compliance with the educational standards and regulations of the department, he has strong communication, leadership, analytical, planning, coordination and relationship management skills. Has undergone for comprehensive training programme of Dental Implants and has various publications with (National and International) Journals.

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PREFACE

Periodontal Medicine book is written in simple language. This book is meant to serve as a guide to the Undergraduate and Postgraduate students and covers all the necessary topics for them. This book may also contain some errors. Suggestions regarding this book is heartily welcome and will be considered. I hope that the textbook will fulfill all the requirements and expectations of the students. I request readers for their suggestions to make this book better.

Dr. Abhishek Verma

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CHAPTER 1

Introduction

Periodontitis, one of the most common disease of humans, is an infectious condition that can result in the inflammatory destruction of periodontal ligament and alveolar bone. Periodontal destruction probably results from the action of various toxic products released from specific pathogenic subgingival plaque bacteria, as well as from the host responses elicited against plaque bacteria and their products. The inflammatory response may result in gingival ulceration around the tooth, which can allow intact bacterial cells or their products including lipopolysaccharides, peptidoglycan fragments, and hydrolytic enzymes into the systemic circulation. It is also known that the host response to periodontal infections results in the local production of cytokines and biological mediators including interleukins and prostaglandins, as well as systemic responses such as induction of serum antibodies.

In light of the extensive microbial plaques associated with periodontal infections, the chronic nature of these diseases, and the exuberant local and systemic host response to the microbial assault, it is reasonable to assume that these infections may influence overall health and the course of some systemic diseases. The systemic ramifications of periodontal infection can be traced back to the largely unsubstantiated theory of focal infection which was promulgated during the 19 early 20th centuries. This theory 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. Miller described the mouth as a "focus of infection" through which "microorganisms or their waste products obtain entrance to parts of the body adjacent to or remote from the mouth." A landmark 1989 paper by Mattila and coworkers reintroduced the association between oral infection and systemic disease using sound, scientific methods. Later studies by DeStefano, Beck, Offenbacher and others have provided exciting support that periodontitis may confer independent risks for systemic conditions, in particular cardiovascular diseases, preterm low birth weight, diabetes and respiratory disease.

There is accumulating evidence that suggest Periodontal infection may influence pregnancy outcomes by providing a source of bacterial components

such as lipopolysachrides, which trigger release of immune modulators and may influence the course of pregnancy. Recently, attention have been received that suggest periodontal disease either predisposes or exacerbate the diabetic condition. A recent epidemiological study has tested the hypothesis that severe periodontitis in persons with non-insulin dependent diabetic mellitus increases the concentration of glycalated hemoglobin in serum (Taylor et al., 1996).These observation suggests that severe periodontitis may be an important risk factor in the progression of diabetes. It is also becoming increasing apparent that potential respiratory pathogens may become established in the oral flora of patients with periodontal disease. These notion is proposed by the observation that medical intensive care unit patients, who tend to have poor oral hygiene offen harbor respiratory pathogens in the dental plaque (Scannapieco et al., 1992). Therefore, potential respiratory pathogens adherent to bacteria in the subgingival plaque of patients with periodontitis may emerge in greater number following treatment with antibiotics (Rams et al., 1990 & Helovuo et al., 1993). These bacteria may than be aspirated to cause respiratory disease, especially in patients with compromised defences.

Several studies have pointed to a possible relationship between chronic oral infection and pathogenesis of various cardio-vascular disease. Indeed, a positive association between the presence of periodontal infection and cardio-vascular disease has been noted with patients with periodontal disease having a 1.5 to 2.0 fold greater risk of increasing fatal cardio-vascular disease than patients without periodontal disease. Infection in general appears to be a risk factor for atherosclerosis. Bacterial products such as lipopolysaccharides likely elicit recruitment of inflammatory cells into major blood vessels, proliferation of vascular smooth muscle, vascular fatty degeneration, and intravascular coagulation. These changes are the result of the action of various biologic mediators, on vascular endothelium and smooth muscle. It may be possible that inflammatory response characteristic of periodontal disease, marked by high levels of inflammatory mediators, exacerbates the process of atherogenesis.

The aim of the present review is to evaluate the current information on the relationship between periodontal disease and various systemic diseases like respiratory, cardio-vascular, preterm low birth weight, and diabetics to determine weather the information is sufficient to conclude that periodontitis is a risk factor for these systemic diseases. To evaluate a possible relationship between periodontal disease and individual systemic disease, each condition has been discussed under

following heading: epidemiological studies, microbiological findings and influence of inflammatory mediators.

The notion that oral or periodontal infection can influence systemic health is not new to dentistry and has been proposed at various times through out the centuries. Oral sepsis was first introduced into the medical literature in a report entitled “Oral sepsis as a cause of disease” by William Hunter in 1990. This was then superseded by focal infection, introduced by Frank Billings in 1912. However. a careful review of the medical literature indicates that the belief that conditions affecting the mouth could have implications on peripheral tissues and organs has been held from the very earliest medical recordings.

The Hebrew book *Sefer Haolsmot O Maaseh Tovia* compared the human body to a house. The mouth was seen as the doorway and must be kept scrupulously clean to protect the body from contamination.Hippocrates (400 BC) described a patient with ‘‘rheumatism” whose arthritis was cured by the extraction of a tooth. In 1768, Thomas Berdmore in *A treatise on the disorders and deformities of the teeth and gums* described the relationship between the teeth and the entire body as one leading to the most “excruciating pains and dangerous inflammations and sometimes deep seated abscesses which destroy neighboring parts and affect the whole system by sympathy, or by infecting the blood with corrupted matter”.

In 1818 one of the most famous physicians in America,Benjamin Rush (a signatory to the Declaration of Independence) reported the course of a disease in which a woman who was suffering from rheumatism of long standing had an aching tooth extracted and “she recovered in just a few days”.

In 1891 Miller published a classic article entitled “The human mouth as a focus of infection”, In this article he endeavors to call attention to the various diseases both local and general, which have been found to result from the actions of micro-organisms which have collected in the mouth, and to the various channels through which these micro-organisms or their waste products may obtain entrance to parts of the body adjacent to or remote from the mouth. He also tried “to establish the great importance of a thorough understanding on the part of the physician, no less than of the dentist, of mouth germs as a factor in the production of disease”, Diseases he felt were able to be traced “to the action of mouth bacteria” included: ostitis, osteomyelitis, septicemia, pyemia, meningitis, disturbance of alimentary tract, pneumonia, gangrene of the lungs, angina Ludovici, diseases of the maxillary sinus, actinomycosis, noma, diphtheria, tuberculosis, syphilis and thrush.

Miller also reported fistulae of dental origin that opened on the neck, shoulder, arm or breast and cites a case report of a 33-year-old woman where the connection of chronic fistula on the breast just above the nipple was discovered by the discharge, on the day following a visit to a dentist, smelling like the medicament used by the dentist in treating a badly diseased root. A solution of cochineal injected into the root also made an appearance at the opening of the fistula a few hours later. The fistula resolved upon extraction of the tooth. Miller stressed that, wherever such germ organisms existed, there was a risk that they could produce "a metastic abscess wherever a point of diminished resistance existed".

In 1990, Dr Hunter wrote an article entitled "Oral sepsis as a cause of disease". In which he states because of oral sepsis that not only is the constant swallowing of pus a most potent and prevalent cause of gastric trouble, but that the catarrh set up is not simply irritant but actually infective, and may lead in time to other more permanent effects - namely atrophy of glands and chronic gastritis and in, certain cases even to suppurative gastritis. However, he did not believe that the effects of oral sepsis were confined to gastritis but also diseases such as tonsillitis, glandular swellings, middle-ear suppurations,ulcerative endocarditis, empyemata, meningitis, nephritis and osteomyelitis.

In 1900, Godlee described how the signs and symptoms of other conditions such as pleurisy and suspected carcinoma of the stomach could be attributed to pyorrhea alveolaris and how all the signs and symptoms disappeared after careful removal of all calculus and regular syringing of the pockets with a hydrogen peroxide solution. In 1902, Colyer described the resolution of irregular heartbeat, gastric effects and "general debility" after the treatment of any oral sepsis present. Other relationships that were put forward by Knight et. Al (1904) were those between oral sepsis and migraine headaches, laryngeal pain and spasm (which could induce cough, loss of voice and wasting), blindness and deafness all which may be cured on, treatment of the oral sepsis.

As the theory of oral sepsis became more popular, theories were put forward by smith et al., (1903) as to which organs were most susceptible to different types of oral sepsis and how the treatment of oral sepsis could lead to recovery from tonsillitis, tuberculosis and diabetes. It was also believed that oral sepsis could be transmitted by the licking of envelopes, use of contaminated telephone receivers and men with beards. In many cases of malnutrition the sole cause was felt to be a "filthy mouth" and that "no greater good could come to humanity than the full

recognition of the dangers from this insidious, prolific, and virulent infection in the human mouth" and that the adoption of proper oral hygiene practices immediate and marked improvement to general health, and in notable increase in the average duration of human life".

In 1911 Frank Billings, Professor of Medicine and head of the focal infection research team at Rush Medical College in Chicago, replaced the term oral sepsis with "focal infection". In the Lane medical lecture delivered in San Francisco in 1915, he defined a focus of infection as a "circumscribed area of tissue infected with pathogenic organisms" and said that the term focal infection implied 1) that such a focus or lesion of infection existed, 2) that the infection was bacterial in nature and 3) that as such it was capable of dissemination, resulting in systemic infection of other contiguous or noncontiguous parts. Billings advocated the removal of all foci of infection and the improvement in patient immunity by absolute rest and improvement of the general and individual hygiene. It was his opinion "that these measures alone will stop the further progress of the disease, and usually entire recovery will take place". A measurement of the clinical benefit of removing focal infection was conducted as a retrospective postal survey in 1917by Huges et. Al (1994). Twenty-three percent of cases reported a cure for their arthritis following removal of infective foci, while another 46% experienced some improvement in symptoms.

Focal infection was also implicated as being a causative factor by Galloway et.al 1931 in miscarriage, pyelitis, mastitis, phlebitis, anemia and toxemia in pregnancy, as well as predisposing to "gastric cancer" (Steadman et al., 1914). Leading members of the medical community such as Charles Mayo of the Mayo Clinic advocated the focal infection theory. He stated that "in children the tonsils and mouth probably carry eighty percent of the infective diseases that cause so much trouble in later Iife". Rosenow advocated that the prevention of oral sepsis in the future, with a view to lessening the incidence of systemic diseases, should henceforth take precedence in dental practice over the preservation of the teeth almost wholly for mechanical or cosmetic purposes, as has largely been the case in' the past Cecil et al., 1938.

What followed in dentistry was the avoidance of conservative dentistry in favor of extractions. There developed a philosophy by which many dentists practiced that came to be known as the "hundred percenter", whereby all teeth that were endodontically (symptomatic, asymptomatic or successfully treated) or

periodontally involved were extracted to avoid a possible focus of infection. The leading spokesperson for this radical approach' was the physiologist Martin H. Fisher from Cincinnati. He regarded a tooth with a root filling as a dead organ. To Fishcr extraction was the only possible way out of what he termed "the dentist' dilemma".

An editorial in *The Dental Cosmos* in 1930 stated that tile policy of indiscriminate extraction of all teeth in which the pulps are involved has been practiced sufficiently long to convince even the most rabid" hundred percenter" that it is irrational and does not meet the demands of either medical or dental requirements, and much less those of the patient. The editorial called for a return to "constructive rather than destructive treatment". The medical community also started to re-evaluate its approach to focal infection. H.C. Cecil. who had been a great proponent of the focal infection theory, published an article in 1938 in which he reported a follow-lip study of 156 patients with rheumatoid arthritis who had teeth and/or tonsils removed because of foci of infection. Of the 52 patients that had teeth extracted, 47 did not get any better and 3 became more ill. Williams & Burket 1951 reviewed a series of papers on focal infection and found that there is no good scientific evidence to support the theory that removal of these infected teeth would relieve or cure arthritis, rheumatic heart disease, and kidney, eye, sin, or other disorders. On the other hand, it is well to keep in mind that if a focus of infection has been found in the mouth, every effort should be made to remove the infection as a general hygiene measure.

Edmund Kells (a pioneer in the field of dental radiology) asserted that conservative treatment might be justifiable but that the danger of focal infection had to be kept in mind. In 1951, the 2nd annual Workshop of the New Jer*sey* section of the American Academy of Dental Medicine considered "Focal infection with relation to dental medicine". Submissions were made by many study groups including periodontology, endodontics, oral surgery, internal medicine and pathology. The reports from this group were inconclusive; the periodontal group stated that "there is a direct relationship between a periodontal condition and an associated systemic problem, particularly in ophthalmology and cardiology", whereas the endodontic group said there was no systemic contraindication for endodontic treatment of teeth, while later stating that endodontics may act as a "trigger area" where there is a base of lowered resistance.

An editorial in the Journal *of Amercian Medical Association* in 1952 stated that the focal infection theory had fallen out of favor because many patients with

diseases presumably caused by foci of infection have not been relieved of their symptoms by removal of the foci. Many patients with these same systemic diseases have no evident focus of infection, and also foci of infection are, according to statistical studies, as common in apparently' healthy persons as those with disease.

A landmark 1989 paper by Mattila and coworkers reintroduced the association between oral infection and systemic disease using sound scientific methods. Later studies by Destefano, Beck, Offenbacher and others have provided exciting support. that periodontitis may confer independent risks for systemic conditions, in particular cardiovascular disease, pre term low birth weight, respiratory disease and diabetes. At the 1996 World Workshop in Periodontics, OfIenbacher introduced the term, "periodontal medicine," as a discipline that focuses on validating this disease' relationship and its biological plausibility in human populations and animal models.

CHAPTER 2

Effect of Periodontal Disease on Preterm Low Birth Weight

The weight of the fetus at birth is the most important variable as far as the survival, growth and healthy development of a child is concerned. According to the World Health Organization, LBW is defined as being less than 2500 g and is a major public health problem in both developed and developing countries. A birth is considered premature if the fetus is born after a gestation period of under 37 weeks. It is generally true to say that the majority of preterm births are also low birth weight. Preterm birth is a major medical, social, and economic problem accounting for a large proportation of maternal and especially neo-natal mortality, acute morbidity, and long term sequelae. In cases of premature birth, the baby's vital organs are immature and incapable of readily adapting to the start of a life outside the uterus.

Despite advances in maternal prenatal care and increased public awareness, the incidence of preterm birth has not changed significantly over the last 40 years. It has been reported (Gibbs et al., 1992, Toth et.al: 1998), that infection during pregnancy is one of the complications frequently associated with preterm delivery. Convincing evidence has associated preterm birth and infection, especially genitorurinary infections, which appear to be an important factor in the premature rupture of membranes. Several studies have linked bacterial vaginosis with preterm birth (Paige et al., 1998, Holst et a1., 1994). However, treatment of vaginosis has not lead to definite conclusions on its efficacy in reducing preterm delivery (Mc Donald et al., 1997, Cariey et al., 2000) and the impact of such interventation on preterm birth rate remains unclear (Villar et al.,1998). Periodontal diseases are a group of infectious diseases resulting in inflammation of gingival and periodontal tissues and progressing loss of alveolar bone. The periodontal infection is initiated and sustained by several bacteria, predominantly gram -ve, and anerobic and microphillic bacteria that colonize the subgingival area. It has been postulated that association between periodontal diseases may be a potential independent risk factor for preterm birth and low birth weight after adjusting for several known risk factor.

Clinical Studies

In several epidemiological studies, the relationship between clinical science of maternal periodontitis and pregnancy outcome have been examined and suggested that maternal periodontitis is an independent risk factor for pre-term birth.

Dasanayake (1998), evaluated the association between the oral health status of pregnant women and the low birth weight of the new born. The effect of periodontal and dental caries status of the woman at the time of delivery on the birth weight of the infant was evaluated by using conditional logistic regression analyses, while controlling for known risk factor for LBW.A match case control study was performed using 55 cases and 55 controls derived from among 503 mothers who delivered their babies in Thailand. Mother who delivered a live infant whose birth weight was less than 2,500 g was considered a potential case. Potential control were mothers who delivered live infants weighted 2,500 g or more. Mother height, lack of prenatal care and the number of healthy sextants in the mouth emerged as independent risk factor for LBW, in the study. Dental caries status or some of the known risk factor for LBW, such as smoking, alcohol, and coffee consumption were not found to be significantly associated with LBW in examined subjects. Conditional logistic regression analyses indicated that mother with more healthy sextants in mouth and those who were taller had a lower risk of giving birth to LBW infants, while mother who did not receive pre natal care had a higher risk of giving birth to an LBW infant. Dental caries status of mother was not a significant risk factor for low birth weight. In was concluded that poor periodontal health of the pregnant women was a potential independent risk factor for LBW.

Offenbacher et al., (1998), conducted study on pregnant or postpartum women. 124 pregnant or postpartum women were included. PLBW cases were mother whose infant had a birth weight of less than 2,500 g and who had one or more of the following: gestational age <37 weeks preterm labour (PTL), or pre term premature rupture of membranes (PPROM). Control were all mothers whose infant had a normal birth weight (NBW). Assessments included a broad range of known obstetric risk factor, such as tobacco usage, drug use and alcohol consumption, level of prenatnal care, parity, genitourinary infection, and weight gain during pregnancy. Each subjects received a full mouth periodontal examination to determine clinical attachment levels. It was found that PLBW cases and primiparous (first birth) PLBW cases had significantly worse periodontal disease than the respective NBW controls. Logistic regression models demonstrated that

periodontitis is a statistically significant risk factor and covariates, for PLBW, with adjusted odds ratio of 7.9 and 7.5 for all PLBW cases and primiparous PLBW cases, respectively. It was concluded that these findings were the first to demonstrate a link between periodontal infection and adverse pregnancy outcomes.

Offenbacher et al., (l999), investigated an association between preterm low birth and periodontal disease in humans. A case control study of 124 pregnant or postpartum mothers were conducted. PLBW cases were identified as <2,500 g along with gestational age <37 weeks due to preterm labor or premature rupture of membranes. Controls were mothers with normal birth weight (NBE) infants. Periodontal status was determined using clinical attachment levels and extent scores. PLBW and primiparous PLBW cases exhibited significantly more clinical attachment loss as compared to NBW controls. Logistic regression models detected a significant, strong association between periodontal disease (i.e., 60% or more of sites with >3 mm attachment loss) and PLBW with adjusted odds ratios of 7.5–7.9. It was concluded that the odds ratios for periodontal disease were numerically higher than other known risk factors like alcohol use, tobacco and maternal age.

Offenbacher et al., (2001), determined whether maternal periodontal disease would contributes to the risk for prematurity and growth restriction in the presence of traditional obstetric risk factors. Periodontal examinations of full mouth were conducted at enrollments a (prior to 26 weeks gestational age) and again within 48 hours postpartum to assess changes in periodontal status during pregnancy. A 3-level disease classification (health, mild, moderate-severe) were used for Maternal periodontal disease status at antepartum and also incident periodontal disease progression during pregnancy were used at exposure for examining association with the pregnancy outcomes of preterm birth by gestational age (GA) and birth weight (BW) adjusting for race, age, food stamp eligibility, maternal status, previous preterm birth, first birth, chorioamnionitis, bacterial vaginosis, and smoking. Interim data from the first 814 deliveries demonstrate that maternal periodontal disease at antepartum and incidence/progression of periodontal disease were significantly associated with a higher prevalence rate of preterm birth, BW <2,500g, and smaller birth weight for gestational age. Among periodontally healthy mother the unadjusted prevalence of birth of GA <28 weeks was 1.1%, it was higher with mother with mild periodontal disease (3.5%) and highest among mothers with moderate severe periodontal disease (11.1%). A similar pattern was seen for increased prevalence of low birth weight deliveries among mothers with

antepartum periodontal disease. For example there were no birth of BW < 1000 g among periodontally healthy mother, but the adjusted rate was 6.1% and 11.4% for mild and moderate severe periodontal disease respectively. They concluded that the study was preliminary in nature, and suggested further consideration of periodontal disease as a potentially new and modifiable risk for preterm birth and growth restriction.

Romero et al., (2002), determined whether maternal periodontal disease (PD) could be associated with the nutritional condition of newborns, controlling the traditional risk factor for premature child birth and low birth weight, like infection during pregnancy. 69 mothers were selected: 13 were periodontally healthy and 56 had varying stages of periodontal disease. Periodontal disease presence and severity were clinically determined using Russell's periodontal index. The nutritional evaluation of the newborns was determined by Lubchenco's modified growth patterns. The average birth weight and gestational age was found to be decreased as the mother's periodontal health was worsened. It was suggests that the variations observed in birth weight and gestational age could be related to the effects of periodontal disease on intrauterine growth and normal gestation periods. Correlation analysis demonstrated a highly significant clinical relationship between more severe periodontal disease and lower birth weight a significant relationship was also clinically demonstrated between increasing periodontal disease severity and decreasing gestational age of the newborn babies. There were significant differences in the weight and gestational age of the newborn of the mother with periodontal disease. It was concluded that periodontal disease in pregnant women may be a significant risk factor for preterm delivery and low birth weight.

Offenbacher et al., (2003), assessed an association between periodontal disease and PT/LBW. 93 mothers were examined who gave birth to preterm or low birth weight children. These were match with 31 control mothers who gave birth to children of normal term and birth weight. They found that the odds ratio for periodontal disease and premature birth were significant, with the risk for PT/LBW 7.5 fold greater if the mother had evidence of periodontal disease. It was concluded that evidence supporting the contention that women with periodontal disease had a greater risk for having preterm or low birth weight children.

LFM et al., (2005), verified the possible association between periodontitis and low birth-weight babies, by examining 151 mothers who gave birth to naturally delivered babies in their case control study. The case group consisted of 76 mothers

who had given birth to babies of gestational age (GA) <37 weeks and weight <2500 g. The control group included 75 mothers who had given birth to babies of gestational age (GA)>37 weeks and weight >2500 g. The periodontal examination included measurements of probing pocket depth (PPD) and clinical attachment loss (CAL) at six sites from all existing teeth, except for third molars. The median number of sites with PPD>4 and CAL>3 was 8% in the test group, and 4% in the control group. The significant association with low birth weight (1bw) were periodontitis (odd ratio (OR) = 3.48,95% confidence interval (CI); 1.17: 10.36), arterial hypertension (OR = 9.65, 95%, CI; 2.22; 41.91), hemorrhage during pregnancy (OR = 10.88, 95%, CI: 0.02; 0.43) and genitor urinary infection (OR = 3.21, 95%, CI:1.25; 8.20). It was concluded that there was an association between the existence of periodontitis and low weight birth along with other cofactor such as number of prenatal examinations, maternal arterial hypertension, genitourinary infection and the presence of hemorrhage during pregnancy.

Lopez et al., (2002), studied the influence of periodontal disease as a risk factor for preterm low birth weight (PLBW). 400 pregnant women with periodontal disease, aged 18–35, were enrolled while receiving prenatal care. These women were randomly assigned to either an experimental group (n=200), which received periodontal treatment before 28 weeks of gestation or to a control group (n=200) which received periodontal treatment after delivery. The primary outcome assessed was the delivery at less than 37 weeks of gestation or an infant weighing less than 2,500g.0f the 400 women enrolled, 49 (37 in the treatment group and 12 in the control group) women (12.7%) were excluded for different reasons. The incidence of PLBW in the treatment group was 1.84% 93/163) and in the control group it was 10.11% concluded that Periodontal disease appears to be an independent risk factor for PLBW and Periodontal therapy significantly reduces the rates of PLBW in this population of women with periodontal disease.

Obstetricians have identified risk factors for prematurity and low birth weight that includes maternal age, socio economic status, inadequate prenatal care, hypertension, tobacco abuse, genitor- urinary tract infections and diabetes. However, efforts to control these risk factors have not resulted in a significant reduction in the number of PLBW birth. Various clinical studies have demonstrated significant relationship between increasing severe periodontal disease and both low birth weight and adverse gestational age. It has been suggested that periodontal disease may be a risk factor, or at least a modifying element. These clinical findings provide information that periodontal disease in pregnant women may be

a significant risk factor for pre term delivery and low birth weight. On examining some of these accumulating evidence, it may be reasonable to assume that maternal periodontal infections could adversely influence pregnancy outcomes.

Microbial Studies

The clinical research examining the relationship between maternal periodontal disease and pre term birth weight suggested that the average birth weight and gestational age decreases as the severity of the mother periodontal disease increases. Periodontal disease is a infectious disease caused by facultative and anaerobic gram -ve bacteria. It has been reported that (Collin et al., 1994) intfection with gram –ve periodontal pathogens may induce adverse effects on the fetus, depending on the degree of infection. The possible mechanism for the association between periodontal disease and prematurity was suggested that microorganisms, their endotoxins, and resulting host inflammatory mediators may enter the uterian cavity from remote site such as the oral cavity either directly or from the blood borne route. There have been repots in both animal model and human that periodontal disease pathogens are associated with pre term pre term and low birth weight.

Arko et al., (1998), studied the effect of exogenous P.gingivalis oral challenge on fetal weight in experimental models of periodontitis in pregnant hamsters. Four groups of animals were fed either control chow one plaque-promoting chow for 8 weeks to induce experimental periodontitis prior to mating. Two groups of animals one control chow, one plaque-promoting chow were also challenged with exogenous Porphyromonas gingivalis. There were no significant effects on fetal weight of P.gingivalis oral challenge under either diet conditions in which the organisms cannot colonize to induce periodontal infection. The mean fetal weights of 1.54g (SE) 14 dams on control diet and 1.54 g for 17 dams on control diet+ P. gingivalis challenge. Neither of these 2 groups developed periodontitis. In contrast, both groups of animals with the plaque-promoting chow, beginning 8 weeks prior to mating, developed periodontitis. The group fed plaque-promoting chow (15 dams) had a mean fetal weight of 1.25 g that was 81.0% of the weight of the control group. The group of 11 dams on both plaque- promoting chow and P. gingivalis gavage also had significantly smaller fetuses. The mean fetal weight for this group was I.20 g, which represented a significant 22.5% reduction in fetal weight, as compared to controls. It was concluded that exogenous P. gingivalis challenge by gastric gavage did not promote either more severe periodontal disease or more severe fetal growth restriction.

Madianos et al., (2001), assessed the maternal periodontal infection using whole chromosal DNA probes to identify 15 periodontal organisms within maternal periodontal plaque sampled at delivery. The study subjects were pregnant women enrolled in the prospective study of Oral Conditions and Pregnancy (OCAP). It was analyzed that all available samples from the first 400 women who completed the study: 386 maternal plaque, 367 maternal serum, and 339 fetal serum samples. Maternal postpartum igG antibody and fetal exposure, as index by fetal cord blood igM level to these 15 maternal oral organisms, was measured by whole bacterial immunoblots. The potential role of maternal infection with specific organisms within 2 bacterial complexs most often associated with periodontitis, conventionally termed" orange" and "red" complexes respectively, to prematurely was investigated by relating the presence of oral infection, maternal igG, and fetal cord igM, comparing full term to preterm. In general the organism of the orange cluster are more prevalent than those of the red cluster, consistent with other population studies of the oral flora. In general the seropositivity of orange organism is higher than that of the red complex. In general there was trend for mother with term infants to have a higher prevalence of serum antibody to both orange and red complex organisms than mother with preterm infants, although differences did not reach statistical significance for any specific organism. There was a 2.9 fold higher prevalence of igM seropositivity for one or more organisms of the orange or red complex among preterm babies, as compared to term babies (19.9% verses 6.9%, respectively). Specifically, the prevalence of positive fetal igM to C. rectus was significantly higher for preterm as compared to full term neonates (20.0% versus 6.3%,) as well as P.intermedia (8.8% verses 1.1%). The highest rate of Prematurity (66.7%) was observed among those mother without a protective red complex igG response coupled with a fetal igM response to orange complex microbes (combined OR 10.3). It was concluded that maternal periodontal infection in the absence of a protective maternal antibody response is associated with systemic dissemination of oral organisms that translocate to the fetus resulting in prematurity.

Dasanayake et al., (2005), evaluated specific oral bacterial levels during pregnancy in relation to gestational age and birth weight while controlling for demographic, medical, and dental variables to test the hypothesis that oral bacteria other than periodontal pathogens are also associated with pregnancy outcomes. The study population consisted of 297 predominantly African- American women who were pregnant for the first time. The salivary bacterial levels evaluated were Streptococcus mutans, Streptococcus sobrinus, Streptococcus sanguinus,

Lactobacillus acidophilus, Lactobacillus casei, Actinomyces naeslundii genospecies (gsp) 1 and 2, total streptococci, and total cultivable organisms. For 1 unit increase in log (10) A. naeslundii gsp 2 levels, there was a 60 gm decrease in birth weight, and a 0.17 week decrease in gestational age. In contrast, per 1 unit increase in log (10) L. casei levels, there was a 42 gm increase in birth weight, and a 0.13 week increase in gestational age. The authors concluded that other oral bacterial species could also be related to pregnancy outcomes in addition to previously reported periodontal pathogens.

Lin et. al (2003), evaluated the effect of infection with the periodontal pathogen *Porphyromonas Gingivalis* on pregnancy outcomes. 20 challenged mice were included. Female BALB/c mice were inoculated with heat-killed *P. gingivalis* (109 CFU) in a subcutaneous chamber and mated 2 weeks later. At gestation day (GD) 7.5, mice were challenged with live *P. Gingivalis* (107 CFU) *(n*= 20) or broth (control; *n*= 8) and sacrificed at gestation day 16.5. Among the 20 challenged mice, 8 had both normal weight and FGR fetuses within the same litter. Of the eight challenged mice with FGR fetuses, three had PCR signals for *P. gingivalis* in liver and uterus, but not in the spleen. Liver, uterus, and spleen were negative for *P. gingivalis* DNA among all other challenged and control mice. In serum of dams with FGR fetuses, tumor necrosis factor alpha levels were elevated significantly, while interluekin-lO levels were significantly reduced compared to levels in dams with normal fetuses. *P. Gingivalis-Specific* serum immunoglobulin G levels were significantly elevated in dams with FGR fetuses compared to dams without any FGR fetuses. It was concluded that *P. Gingivalis-induced* murine FGR is associated with systemic dissemination of the organism and activated maternal immune and inflammatory responses.

Yeo et al., (2005), determined the effects of Campylobacter rectus infection on pregnancy outcomes in a mouse model. Pregnant mice were randomly assigned to one the three treatment groups of eight animals each. On embryonic day (E) 7.5, pregnant mice in the control group received an intrachamber injection of 0.1 ml of phosphate buffered saline (PBS), while the pregnant mice in the test groups received an intrachamber injection of 0.1 ml of either 107CFU/ml or 109CFU/ml live Campylobacter rectus strain. They were sacrificed on E 16.5 and fetuses were evaluated for stage of development, weight, and crown-rump length. Dams receiving C. rectus had more fetal resorptions after challenge with 107or 109 CFU/ml (24.1% and 30.1%, respectively) than controls (9%). Higher numbers of growth-restricted fetuses were also observed in the Campylobacter rectus

challenged groups (21%) as compared to controls (2.3%). Fetuses from dams challenged with 109 CFU/ml weighed less (0.49 g) and had shorter crown rump lengths (14.69 mm) than controls (0.53 g; 15.54 mm). Campylobacter rectus was detected by polymerase chain reaction in the placentas from both treated groups and in maternal liver tissues from the 109 CFU/ml challenged group. The authors concluded that subcutaneous maternal Campylobacter rectus infection increased fetal resorption and fetal growth restriction in a mouse model.

Han et. al (2006), studied the transmission of an uncultivated *Bergeyella* strain from the oral cavity to amniotic fluid in a case of preterm birth. A total of 35 pregnant women undergoing transabdominal amniocentesis were recruited. Three samples were collected at the time of recruitment: AF, blood, and vaginal swabs. AF was placed directly into sterile 15 ml coming centrifuge tubes. The subgingival plaque samples were collected at the time of recruitment. AF samples were divided into I-ml aliquots. The vaginal swabs were suspended in sterile phosphate-buffered saline. All samples were then centrifuged at 10,000xg for 3 min. One patient was excluded from the study due to an error in sample collection. For the remaining 34 patients, the population consisted of 50.0% African-American, 35.3% Caucasian, and 14.7% Hispanic subjects, with an average age of 26.6 years. On the basis of the reasons for amniocentesis, the patients were divided into three groups: group 1, patients in preterm labor (PTL) or threatening PTL, including those undergoing cerclage due to an incompetent cervix (19 patients); group 2, patients checking for fetal lung maturity (11 patients); and group 3, patients interested in fetal genetic diagnosis (4 patients). Among group 1 patients, approximately 58% delivered before 35 weeks of gestation, with five delivering extremely early, before 30 weeks of gestation. The rates of premature delivery before 35 weeks were lower in groups 2 and 3, at 0% and 25%, respectively. The blood samples collected from the 34 patients showed no bacterial growth in any samples. The AF samples were analyzed by PCR using universal primers 785F and 422R. Bacteria were detected only in patient 14. The other patients were either not infected or infected at a subclinical level not detected by PCR. Bacterial DNA was amplified from the only patient with clinical intrauterine infection and histologic necrotizing acute and chronic chorioamnionitis. One strain, *Bergeyella* sp. clone AFI4, was detected and was 99.7% identical to a previously reported uncultivated oral *Bergeyella* strain, clone AK152, at the 16S rRNA level. The same strain was detected in the subgingival plaque of the patient but not in her vaginal tract. The 16S-23S rRNA sequence of clone AFl4 matched exactly with the sequences amplified from the

patient's subgingival plaque. *Bergeyella* spp. had not been previously associated with preterm birth and were detected in subgingival plaque of women without clinical levels of intrauterine infection. Thus, it was concluded that there was a possible link between oral bacteria and preterm birth.

Leon et al., (2007), examined the microbial invasion of the amniotic cavity by periodontopathic bacteria in pregnant women with a diagnosis of threatened premature labor. Twenty-six women with threatened preterm, premature labor and a gestational age ranging between 24 and 34 weeks were included. Clinical parameters included all teeth (excluding third molars) and included clinical attachment level (CAL), probing depth (PD), supragingival plaque accumulation, and bleeding on probing (BOP).Samples collected from amniotic fluid and from four deepest periodontal pocket in each patient were pooled in prereduced transport fluid and cultured. Amniotic fluid or plaque samples were homogenized, DNA was extracted, and polymerase chain reaction (PCR) amplification of 16SrRNA with specific and universal primers was carried out. Twenty six women with threatened premature labour were enrolled: eight patients with preterm premature rupture of membrane and 18 with preterm labour with intact membranes. 8 women with gingivitis, 12 with periodontitis, and 6 without periodontal disease were studied. Subgingival plaque samples including P. gingivalis were found in 50% of patients. The prevalence of patients with periodontal disease with P. gingivalis was 50%. In women with gingivitis, the occurrence of P. gingivalis was 50.0%. In patients with chronic periodontitis, the prevalence was 50.0%. All amniotic fluid samples examined by bacterial culture were negative for P. gingivalis. The prevalence of patients with microbial invasion of amniotic cavity by P. gingivalis detected by PCR was 30.8%. All colonies showed the identification of periodontal pathogens by PCR in the amniotic cavity. It was concluded that the presence of microbial invasion of the amniotic cavity by P.gingivalis could indicate a role for periodontal pathogenic bacteria in pregnant women with a diagnosis of threatened premature labor.

Human cross sectional and case control studies as well as animal experiments have shown periodontitis as a potential risk for reduced fetal rate, preterm birth, or other pregnancy complications. Periodontal pathogens viz Porphyromonas gingivalis, Campylobacter rectus, P. forsythus, P. intermidia, P. nigrescens, T. denticola and F. nucleatum have been reported significantly higher in plaque of pre term group. Human studies in patient with periodontitis and animal studies have suggested P. gingivalis may be an important component in linking periodontitis to pre term birth. Recently P. gingivalis within the amniotic fluid among pregnant

women with a diagnosis of therened premature labor has been observed. Similar observations are made in mice where haematogenous infections with orally relater Physiobacterium nucleuteum resulted in localized infection in the placenta, causil1gpre term and term stillbirth of the fetal pups. Hanks et al., reported the identification of uncultivated oral bergeyella sp. strain associated with pre term birth and the possible source of infection. It is possible that periodontal disease may fascilitate the oral- utero transfer because of the increased bacterial load in the oral cavity and the altered host immune responses during disease.

Pro Inflammatory Mediators

Recently few studies have examined the association between periodontal disease and pre term birth by exploring the underlying microbial and antibody responses associated with oral infections. Medinos et al., 2001, reported that maternal antibodies through oral organisms could be associated with a decreased rate of pre term delivery and an increase in birth weight and therefore, provided protection to mother and fetuses from exposure to bacterial dissemination. The possible mechanism for association between periodontal disease and prematurity was suggested that the microorganisms, there endotoxins and resulting host inflammatory mediators may enter the uterine cavity from remote site such as the oral cavity either directly or from the blood borne route which may either result in prostaglandin production or direct uterine contraction that can lead to cervical dilation. The dilated cervix may allow further entry of bacteria, there products and cytokines to the uterine cavity until pre term delivery and or premature rupture of members occurs. Therefore, to understand possible mechanism or pathways linking oral infection to pre term birth, recently various studies have explored the maternal antibody responses and pro inflammatory responses associating with oral infections.

During gram -ve infections, several inflammatory mediators like TNF-a, IL-6, IL-l and IL-8 are produced which in turn leads to activation of prostaglandin synthesis. However, TNF-α and PGE2 increases the amniotic fluid during normal pregnancy and are believed to mediate routine parturition. It has been suggested that during infection, abnormally high level of these mediators may lead to premature termination of pregnancy with concomitant low birth weight.

Offenbacher et al., (1999), evaluated the microbial dimension of the periodontitis-PLBW association. Fetal cord blood samples from 21 PLBW and 39 NBW infants were collected and analyzed for the presence of igM specific

antibody against 13 periodontal pathogens using checkerboard immunoblotting. While 17.9% of fetal cord blood samples from NBW infants tested positive for IgM directed against the tested pathogens, 33.3% of PLBW samples tested positive. IgM was most commonly specific for Campylobacter rectus followed by P. gingivalis and Fusobacterium nucleatum. The data indicated that fetal cord blood igM directed against specific periodontal pathogens could be detected in both PLBW and NBW infants. It was concluded that specific fetal immune responses to periodontal pathogens provide direct evidence that maternal periodontal infection can provide a systemic challenge to the fetus in utero.

Lin et al., (2007), determined whether there is an association between pregnancy outcome, oral bacterial load, and maternal humoral responses using data from a recent interventional trial following the delayed-treatment control group of 31 subjects with periodontal diseases. The levels of eight oral bacteria and the maternal immunoglobulin G (IgG) responses in serum to these bacteria were measured at antepartum and postpartum visits to determine the relationship to cases (preterm delivery < 37 weeks' gestation) and controls (term delivery). The results showed that at antepartum, the levels of periodontal pathogens tended to be higher in the preterm (case group) deliveries compared to the term deliveries (control group). Maternal anti-Porphyromonas gingivalis IgG was significantly lower in the preterm group compared to the term group. Postpartum, levels of P. gingivalis, Tannerella forsythia, Prevotella intermedia, and Prevotella nigrescens were statistically significantly higher in preterm births compared to term deliveries. Also, the effects of red and orange microbial clusters were significantly higher in the preterm group compared to the term group. The authors concluded that high levels of periodontal pathogens and low maternal IgG antibody response to periodontal bacteria during pregnancy were associated with an increased risk for preterm delivery.

Offenbacher et al., (1999), examined the effect of P.gingivalis challenge on pregnant hamsters with experimental, periodontitis models. Four groups of animals were fed either control diet or plaque-promoting chow for 8 weeks to induce experimental periodontitis prior to mating. One control diet group and one plaque-promoting chow group were challenged with exogenous P. gingivalis by gastric gavage. No significant effects of P.gingivalis challenge for either diet condition was detected. In contrast, both groups of animals fed the plaque-promoting diet exhibited evidence of periodontitis and significantly smaller mean litter weights. It was concluded that animals with the dietinduced periodontitis

demonstrated significant elevation in intra-amniotic fluid concentration of PGE2 and TNFa, immuno-inflammatory mediators that can induce uterine contraction, cervical dilation, labor and abortion.

Offenbacher et al., (1999), compared the local host response with periodontal flora between cases and controls. 25 PLBW cases and 15Nbw controls were selected. Gingival crevicular fluid (GCF) was collected and assayed for concentration of PGE2. Subgingival plaque samples were obtained from mothers and analyzed for four periodontal pathogens using checkerboard DNA-DNA hybridization techniques. The mean GCF-PGE2 levels for NBW controls were 62.6 ng/ml, mean GCF-PGE2 levels for PLBW cases were 131.4 ng/ml and were significantly elevated. In addition, a significant inverse relationship was observed between the log GCF-PGE2 and birth weight among primiparious mothers. It was concluded that higher levels of the pathogens, P. gingivalis, B. forrsythus, A.actinomycetemcomitans and T. denticola were detected among the PLBW cases.

Collins et al., (1994), assessed the effects of various localized, nondissemination challenges of Porphyromonas gingivalis on inflammatory mediator production and pregnancy outcome in the golden hamster. In the first series of experiments, nonpregnant female hamsters were used to study the effects of P. gingivalis challenge on PGE2 and TNF-a response. After placing subcutaneous chambers, four groups of six animals received one of the following treatments: (i) control (culture broth only), (ii) HKP. Gingivalis (HK), (iii) live P. gingivalis (Live), or (iv) HK P. gingivalis initially, followed by live P. gingivalis 21 days later (HK-Live). Chamber fluids were collected at baseline and 1 and 5 days post challenge for the analysis of PGE2 and TNF-a In the second series of experiments, those same four treatments were performed. All P. gingivalis challenges caused a significant increase in chamber PGE2 and TNF-α at the following order of potency: HK < Live < HK+Live. The HK+Live challenge, PGE2 levels increased from 4.7 pg/ml at baseline to 362 pg/ml at day 5 and TNF-α increased from 26.4 pg/ml to 724 pg/ml at day 5. The same order of potency of the various challenges was maintained with regard to the toxic effects of P. gingivalis on pregnancy outcome. For the HK+Live challenge, fetal weight was decreased 24%, embryolethality increased to 26.5% and the percent fetal resorption increased to 10.6% compared with control animal levels. There was a statistically significant association between increasing levels of both PGE2 and TNF-α and fetal growth retardation and embryolethality. It was concluded that infections with gram-negative periodontal pathogens can elicit adverse pregnancy outcomes and that the levels of PGE2 and TNF-a produced as a result of challenge are associated with the severity of fetal effect.

Roberts et al., (2004), assessed that periodontitis vaccine decreases local prostaglandin E2 levels in a primate model. Interleukin-l fl, tumor necrosis factor alpha, prostaglandin E2 (PGE2), and *Porphyromonas gingiva*lis-specific immunoglobulin G levels in gingival crevicular fluid were measured in primates immunized with a *P. gingivalis* vaccine followed by ligature-induced periodontitis. Only PGE2 levels were suppressed in immunized animals versus controls. A significant correlation was also found between PGE2 levels and decreased bone loss scores. It was concluded that the study presented the first evidence of a potential mechanism involved in periodontitis vaccine-induced suppression of bone loss in a nonhuman primate model and offers insight into the role of PGE2 in periodontal destruction.

Terrone et al., (2001), studied the effect of intra-uterine infusion of interleukin-10 preterm delivery in rats treated with endotoxin. Timed pregnant rats *(n=32)* were received on day 12 or 13 of gestation (term = 22 days). All rats underwent laparotomy with placement of an intrauterine catheter in the distal region of one uterine horn. The rats were randomly assigned, with eight in each group to receive saline, 50 mg lipopolysaccharide, 50 mg lipopolysaccharide with 500 mg interleukin-l0,or 50 mg lipopolysaccharide followed 24 hours later by 500 ng interleukin-10. Calculation'was done to obtain a power of 80%, assuming a 24-hour difference in the treatment to delivery times between the test and control subjects, at least six animals were needed in each group. The lipopolysaccharide group displayed a reduced interval from treatment to delivery compared with both the lipopolysaccharide plus interleukin-l0 groups and the saline controls. No difference in the number of live pups born to the rats receiving either lipopolysaccharide plus interleukin-IO or those receiving saline occurred. In contrast, the lipopolysaccharide endotoxin-treated rats delivered fewer live pups per litter than any of the other three treatment groups. The infusion of lipopolysaccharide alone resulted in a reduction in the birth weight of the pups compared with the saline controls. In contrast, no statistical difference in the birth weight between the lipopolysaccharide plus interleukin-IO groups and the saline-infused controls was found. It was concluded that interleukin-IO appears to be effective in preventing endotoxin-induced preterm birth and fetal wastage in pregnant rats.

Periodontitis is a group of infectious diseases, characterized by an inflammatory reaction, which results in the destruction of the dental attachment apparatus. It is the major cause of tooth loss in adults over the age of 35. The primary etiologic factor for periodontal diseases is bacteria that accumulate in the

gingival sulcus, among which *Porphyromonas Gingivalis* is thought to be one major periodontal pathogen. Clinical studies have documented a strong association between the presence of *P. gingivalis* and periodontal destruction (Socransky, S. S, and A. D. Haffajee. 1992.), and patients with periodontitis often exhibit high titers of antibodies against *P.gingivalis (Okuda, K., T. Saito, K. Hirai, K. Harano, and T. Kalo.* 1994). This microorganism possesses numerous virulence factors, which have been suggested to play an important role in periodontal diseases (Holt, S. C., and T. E. Bramanti. 1991).

The key to resolving the dilemma of preterm birth may lie in obtaining a better understanding of the processes involved. As we better understand the role that cytokines play in preterm labor with infection, new approaches to treating these women may be developed. Interleukin-l0 was originally described as a factor produced by class-2 T-helper cells that suppressed in-flammatory cytokine production and proliferation by class-l T-helper cells. Several line s of experimental evidence support the hypothesis that the ratio of class-l T-helper (inflammatory) to class-2 T-helper (antiinflammatory) cytokines may be critical to pregnancy immunotolerance. It was hypothesized that interleukin-l0 may suppress the inflammatory cytokine production by macrophages and other cell types that occurs in the setting of maternal infection.

This action of interleukin-l0 is likely mediated through a suppression of cytokine-derived prostaglandin production. This concept is supported by in vitro studies in which cytokine-induced prostaglandin production by human amniotic cells was suppressed by interleukin-lO (Bennett WA, Lagoo-Deenadayalan S, Whitworth NS, Stopple lA, Barber WH, Hale E:1994 & Rivera DL, Olister SM, Liu X, Thompson lH, Zhang Xl, Penmoline K:19985.~In addition, interleukin-lO also decreased tumor necrosis factor-a and interleukin-6 release from lipopolysaccharide-treated human arnniochorionic membranes. Additionally, with increasing evidence suggesting an association between amniotic fluid infection and cerebral palsy in humans, the effects of prolonging pregnancy in the setting of infection may be detrimental (Yoon BH, lun lK, Romero R, Park KH, Gomez R, Choi lH, et al.,1997). Finally, we believe interleukin-10 has shown promise as a cytokine-based tocolytic agent for preventing preterm birth when infection is present.

Periodontitis is a group of infectious diseases, characterized by an inflammatory reaction, which results in the destruction of the dental attachment apparatus. Human cross sectional and case control studies as well as animal experiments have shown periodontitis as a potential risk for reduced fetal rate, pre term birth, or other pregnancy complications. Obstetricians have identified

risk factors for prematurity and low birth weight that includes maternal age, socio economic status, inadequate prenatal care, hypertension, tobacco abuse, genitor-urinary tract infections and diabetes. Various clinical studies have demonstrated significant relationship between increasing severe periodontal disease and both low birth weight and adverse gestational age. Human studies in patient with periodontitis and animal studies have suggested P. gingivalis may be an important component in the under linked association in linking periodontitis to pre term birth. Hanks et al., reported the identification of uncultivated oral bergeyella sp. Strain associated with pre term birth as the possible source of infection. It is possible that periodontal disease may fascilitate the oral-utero transfer because of the increased baderialload in the oral cavity and the altered host immune responses during disease. As we better understand the role that cytokines play in preterm labor with infection, new approaches to treating these women may be developed. Interleukin-IO was originally described as a factor produced by class-2 T-helper cells that suppressed inflammatory cytokine production and proliferation by class-l T-helper cells. It was hypothesized that interleukin-10 may suppress the inflammatory cytokine production by macrophages and other cell types that occurs in the setting of maternal infection. It has been suggested that periodontal disease may be a risk factor, or at least a modifying element.

Diabetes mellitus (DM) and periodontitis are common chronic diseases in adults. Both diseases are highly prevalent in the world population. Diabetes mellitus is one of the group of metabolic diseses characterized by the triad of symptoms including polydypsia, polyuria, and polyphagia due to hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Based on these condition, diabetes mellitus can be classified into two main types: type 1 diabetes mellitus which is caused by destruction of the pancreatic β cells that are known to produce insulin; type 2 diabetes mellitus results from defect in insulin molecules or from defective cell receptors for insulin. This defect indicates impared insulin function (insulin resistance) rather than deficiency or lack of production. Similarly, the major complications of diabetes, which include retinopathy, nephropathy, neuropathy, and circulatory abnormalities, are the result of hyperglycemia. Two possible mechanisms for these complications have been proposed. The first is the polyol pathway, where glucose is reduced to sorbitol by the enzyme aldol reductase. Sorbitol is considered a tissue toxin and has been implicated in most of the complications of diabetes (Robinson et al., 1983). The second mechanism is the production of advanced glycation end products (AGEs) due to the non-enzymatic addition to of hexoses to proteins, which causes alterations of many of the body proteins, function like collagen, hemoglobin, plasma albumin, lens proteins, and

lipoproteins (Brownlee et al., 1992). The control of diabetes is therefore directed at controlling the blood glucose levels within normal limits, and there is clear evidence that complications can be prevented by the meticulous control of hyperglycemia. The monitoring of the effectiveness of control of hyperglycemia is formed by measuring the levels of glycated serum protein, especially glycated α-hemoglobin (HbA1c), which because of its incorporation into the red blood cells, gives an indication of the serum glucose levels over the preceding 2 to 3 months.

Patients suffering from diabetes mellitus are known to have increased susceptibility to certain infections. Infection, as they lead to poor metabolic control in diabetes, are of great concern, since it has been shown that hyperglycemia and poor metabolic control result in increased diabetic complications of the eye, kidney, and nerves. Two case series have reported an effect of periodontal treatment on level of glycemia in poorly controlled diabetic patients with periodontitis (Williams et al., 1992). These reports lead to the hypothesis that successful management of periodontal infection in diabetes will lead not only to reduction of the local signs and symptoms of the disease, but also to better control of glucose metabolism. Periodontitis in adult is a bacterial infection caused by gram-negative anaerobes, which populate the subgingival plaque. These putative pathogens include Porphyromonas gingivalis, Prevotella intermedia, Bacteroides forsythus and spirochetes (Slots and Genco 1984). The chronic Gram-negative infection of periodontal origin has been considered a potential focus of infection that may aggravates metabolic control in patients who have diabetes (Soskoline et al., 1998). In this context, the virulence of the subgingival bacteria present in the periodontium gains a greater significance.

There have been numerous studies that have found a positive relationship between poor glycemic control in persons with type 2 Diabetes mellitus and increased periodontitis (Bissada et al., 1982, Sorsa et al., 1992, Tervonent et al., 1993, Mendieta et al., 1993, Saflam-Seppla et al., 1992). Conversly, limited data is available suggesting that periodontitis affects glycemic control in individuals with type 2 Diabetes mellitus. It is known that infections are often accompanied by tissue insulin resistence (Vki-Jarien 1989). A recent study has demonstrated that during the acute phase of bacterial infection, insulin resistance increased by 33%, whereas during the convalesce period it increased by 28% (Sammalkorpi;1998). Moreever, Grossi et al., (1996) have suggested that chronic gram-negative infections and chronic endotoxemia, such as is seen in periodontal disease could also induce insulin resistance and a worsening of metabolic control in diabetic patients.

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CHAPTER 3

Effect of Periodontal Disease on Diabetes

In recent years, the potential of periodontal disease (PD) to cause disturbances in systemic health has been discussed extensively. Studies have indicated that Periodontal disease associated immunologic mechanisms, besides being able to break down local tissues, may also be able to influence systemic conditions such as diabetes and cardiovascular disease (Renvert, 2003). In a 2-year longitudinal trial, diabetic subjects with severe periodontitis at baseline had a six –fold increased risk of worsening of glycemic control over time compared to diabetic subjects without periodontitis (Taylor et al., 1996). Periodontitis may also be associated with increased risk of other diabetic complications, as seen in a longitudinal case-control study in which 82% of diabetic patients with severe periodontitis experienced the onset of one or more major cardiovascular, cerebrovascular, or peripheral vascular events compared to only 21% of diabetic subjects without periodontitis (Thorstensson et al., 1996). Becauses cardiovascular diseases are so widely prevalent in people with diabetes, a recent longitudinal trial examined the effect of periodontal disease on overall mortality and cardiovascular disease-related mortality in more than 600 subjects with type 2 diabetes (Saremi et al., 2005). In subjects with severe periodontitis, the death rate from ischemic heart disease was 2.3 times higher than in subjects with no periodontitis or mild periodontitis, and the mortality rate from diabetic nephropathy was 8.5 times higher in the severe periodontitis group after accounting for other known risk factors. The overall mortality rate from cardio-renal disease was 3.5 times higher in subjects with severe periodontitis.

Carla et al., (2006), assessed the effect of periodontal disease on diabetes metabolic control in a new model for type 2 diabetes-associated periodontal disease. 24, three month-old male GK rats and 24, three month-old male Wister rats were used. Periodontal disease was induced by placing ligature around maxillary second premolar and the animals were followed for 6 weeks. Serum insulin, glucose, and free fatty acids levels were evaluated; interleukin (IL)-1β, IL-6, and tumor necrosis factor-α were measured in adipose tissue supernatant; glucose tolerance and insulin resistance were calculated. Further, alveolar bone

destruction was estimated morphometrically and radiographically. Rats with diabetes + periodontal disease became almost 30% more glucose intolerant and presented a 25% increase in IL-lβ in adipose tissue compared to rats from the diabetes group. Moreover, periodontal disease associated with diabetes resulted in more alveolar bone destruction in comparison to periodontal disease in the absence of diabetes. It was concluded that experimental periodontal disease induced an increase in glucose intolerance and in IL-l β in adipose tissues from diabetic rats, which brings other insight into the importance of periodontal disease for diabetes. Periodontal disease was associated with an increase in serum FFA levels.

Using a type 1 diabetic rat model, Holzhausen et al., 2004, found that diabetic animals with ligature-induced periodontal disease presented an increase of 40% in fasting blood glucose. However, fasting glucose was not as effective as an OGTT in detecting abnormality of glucose tolerance (Lepor, 2004). Thus it could be interpreted as a sign of systemic repercussion of experimentally induced periodontal disease. The major cause of diabetes-associated complications is likely to be sustained hyperglymia (Diamond,2003),the apparent capacity of experimental periodontal disease to alter glucose status brings further insight into the importance of periodontal disease for the diabetic condition.

On the basis of the observation that inflammatory states may influence insulin resistance (IR), the periodontal disease (PD) may affect the metabolic control of diabetes patients (Grossi et al., 1998). In a respective study in humans, Satio et al., 2004 indicated that the presence of deep pockets was associated with the development of glucose intolerance. However, the author were unable to answer the question of whether periodontal pocket were a cause or a result of impaired glucose tolerance. Further, a study reported that experimental periodontal disease increased blood glucose levels in streptozotocin-induced type 1 diabetic rats (Holzhausen et al., 2004). Although these studies have brought insight into the significance of periodontal disease for type 1 and 2 diabetes, the nature of this relation is still unclear and more information is needed.

The Effect of Periodontal Therapy on Metabilic Control in Diabetic

Williams and Mahan, (1960) demonstrated several decades ago that periodontal therapy improves metabolic control, as indicated by reduced insulin requirements and reduction of blood glucose. Several studies addressed the effect of periodontal

treatment on glycemic control of diabetic patients (Miller et al., 1992, Grossi et al., 1997, Christgau et al., 1998, Gustke et al., 1999, Taylor 1999). The outcome of these studies was that periodontal treatment improved the periodontal status in diabetic patients but the improvement in metabolic control was reached only when mechanical periodontal treatment and systemic antibiotics were used. A reduction of glycated hemoglobin in type 1 diabetes patients after periodontal therapy and systemic antibiotics was demonstrated by Williams and Mahan (1960) and Miller et al., (1992). Similar results with systemic application of doxycycline in type 2 diabetes patients were found in the study of Grossi et al., (1997).

It was shown previously that diabetic and non-diabetic patients respond similarly to non-surgical periodontal therapy (Tervonen et al., 1991). However, non-surgical therapy alone was found to be ineffective in reduction of glycemic control in 2–4 month observation periods (Aldridge et al., 1995, Smith et al., 1996, Grossi et al., 1997, Christgau et al., 1998).

Christgau M et al., (1998), assessed clinical, microbiological, medical, and immunological effects of non-surgical periodontal therapy in diabetics and healthy controls. 20 IDDM (insulin dependent, n = 7) or NIDDM (non-insulin dependent, n = 13) diabetic patients (median duration 11.5years, range of HbA1c: 4.4-10.6%) with moderate to advanced periodontal disease and 20 matched healthy control patients, were subjected to supragingival pretreatment and subsequent subgingival therapy. Periodontal examination included approximal plaque index (API), papilla bleeding index (PBI), bleeding on probing (BOP), probing pocket depth (PPD), probing attachment level (PAL). Microbial examination (culture), medical routine examination, and immunological examination (oxidative burst response of PMNs to TNF-a and FMLP) were performed at baseline, 2 weeks after supragingival, and 4 months after subgingival therapy. After completion of 4 months non-surgical therapy, the following baseline clinical parameter in diabetic patients were compared with conyrol patients were as follows: API (30.4% versus 36.3%); PBI (22.9% versus 24.2%); BOP (39.5% versus 46.9%). The median% per patient of pockets with PPD ≥ 4 mm decreased from 41.9%–28.% in diabetics, and from 41.6%–31.8% in controls. Microbiologically, similar reductions of periopathogenic bacteria were found in diabetics and controls. Neither periodontal data nor the oxidative burst response of PMNs showed any significant difference between diabetes and control patients. It was concluded that metabolically well-controlled diabetics might respond to non-surgical periodontal therapy as well as healthy control patients.

Stewart et al., (2001), assessed the effect of periodontal treatment on glycemic control in patients with type 2 diabetes mellitus. 36 patients with type 2 DM (treatment group) received therapy for adult periodontitis during an 18 month period. A 36-person control group was randomly selected from the same population of person with type 2 DM who did not received periodontal treatment. The HbA1c levels in the treatment group decreased from 9.5–7.6 following completion of dental treatment. HbA1c levels in the control group also decreased from 8.5–7.7 and both changes were statistically significant. Furthermore, the difference in changes between the 2 groups was statistically significant. Out of the 36 subjects in each group, 10 control subjects and 5 treatment subjects had virtually no change in HgA1c levels over the 10-month period of investigation. Glucose control worsened in 10 control subjects and 4 treatment subjects during this period. In contrast, 16 control and 27 treatment subjects markedly improved glucose control. During the nine-month observation period, there was a 6.7% improvement in glycemic control in the control group when compared to a 17.1% improvement in the treatment group, a statistically significant difference. Several parameter that could confound or moderate this glycemic control were explored. It was concluded that periodontal therapy was associated with improved glycemic control in persons with type 2 DM.

Faria et al., (2006), compared the response of conventional periodontal treatment between patients with or without type 2 diabetes mellitus from a clinical and metabolic standpoint for 6 months. The conventional periodontal treatment including scaling and root planning were performed, and the response to the treatment was compared between the groups at 3 and 6 months, by the measuring the plaque index, bleeding on probing, probing depth, level of clinical attachment, and gingival recession. In the diabetic patients, the clinical response was related to measurements of HbA1c and glucose in blood at 3 and 6 months. The groups did not significantly differ in plaque index, bleeding on probing index, gingival recession, or clinical attachment level at any examination time. The improvement observed in blood HbAlc levels confirmed a positive metabolic response to periodontal treatment, with a lower value for this variable at each measurement time. It was concluded that both groups of patients showed a clinical improvement after basic non-surgical periodontal treatment, and the diabetic patients showed improved metabolic control (lower HbA1c) at 3 and 6 months after periodontal treatment.

A recent study of Kiran et al., 2005, on well controlled type 2 diabetic patients who had only gingivitis or mild, localized periodontitis examined the effects of

scaling and localized root planning without systemic antibiotics. A diabetic control group with a similar level of periodontal disease received no treatment. Following therapy, the treated subjects had a 50% reduction in the prevalence of gingival bleeding and a reduction in mean hemoglobin A1c from 7.3%–6.5%. The control group, which received no periodontal treatment, had no change in gingival bleeding, as expected, and no improvement in hemoglobin A1c. These results suggest that changes in the level of gingival inflammation after periodontal treatment may be reflected by changes in glycemic control.

In more recent times, treatment has usually consisted of scaling and root planning either alone or in combination with adjunctive systemic tetracycline antibiotics. Tetracycline decreases the production of MMPs such as collagenase and are a logical choice for study because collagenase production is often elevated in diabetic patients (Golub LM, Lee H-M, Ryan ME; 1998).

The study carried out on the NIDDM by Grossi et al., (1997), patients followed 85 subjects over a 1 year post-treatment period. The patients were divided into 4 treatment groups. All 4 groups received scaling and root planning using an ultrasonic scalers, which delivered 1 of 3 different irrigating solutions during therapy, followed in 3 of the 4 groups by 14 days of systemic doxycycline therapy. In all 3 groups that had received systemic doxycycline, a significant reduction in HbA1c was noted after 3 months regardless of the irrigant used during scaling and root planing. This effect was lost at the subsequent 6-,9-,and 12 month visits. This study supports the hypothesis that anti-inflammatory therapy can help in the metabolic control of diabetes.

Lwamoto et al., (2001), evaluated the effects of antimicrobial periodontal therapy on serum TNF- α concentration and subsequent metabolic control of diabetes. 13 type-2 diabetes patients with periodontal disease were enrolled in the study. These patients were treated with local minocycline administration in every periodontal pocket around all existing teeth once a week for a month. Before and after treatment, the number of total bacteria in the periodontal pockets and circulating TNF- α concentration were measured and the HbA1c value was assessed. Following periodontal therapy, the total number of bacteria varied from 10- fold to 10,000-fold. Although not statistically significant, mean probing depth in each subject also decreased, by an average of 0.48 mm. Serum TNF- α concentration decreased from 3.768–3.278. However, in patient G, serum TNF- α concentration increased from 2.626pg/ml to 2.877pg/ml. The average reduction

in TNF- α was 0.49pg/ml. In addition, the HbA1c value was significantly reduced from 7.962–7.123. The average reduction in HbA1c was 0.8%. It was concluded that, antimicrobial periodontal treatment reduces circulating TNF- α which subsequently reduces circulating insulin concentration and HbA1c level. Thus, increased TNF- α caused by chronic inflammation may have an additive effect on insulin resistance in type-2 diabetes patients. Thus it was suggested that controlling periodontal infection plays an important part in the overall management of type-2 diabetes.

Debora C et al., (2003), monitored the effect of non-surgical periodontal therapy on glycemic control in patients with type 2 diabetes mellitus (DM). 30 type 2 DM subjects with periodontitis were randomly divided into two groups. Group 1 (G1), 15 subjects, received one-stage full-mouth scaling and root planning (FMSRP) plus amoxicillin/clavulanic acid 875 mg; group 2 (G2), 15 patients, received only FMSRP. At baseline and after 3 months, the glycated hemoglobin (HbAlc) values, fasting glucose, and clinical parameters were recorded. Following therapy, the subjects were enrolled in a 2-week interval maintenance program for 3 months. The HbAlc values were reduced for both groups, however, the reduction in HbA1c, values for the G2 groups were statistically significant but not for the G1 group. The differences in HbA1c levels were 0.3% and 1.2% for G1 and G2, respectively with a statistically significant difference between the groups. A correlation was found between changes in HbA1c levels and the baseline HbA1c levels and final glucose (r=0.938). The baseline mean fasting glucose levels for both groups were statistically different G1, 221 mg/dl and G2, 175 mg/dl. At the 3month visit, fasting glucose level were 210 mg/dl and 188 mg/dl for G1 and G2, respectively; however the changes were not statistically significant. The changes in fasting glucose levels were not significant for either group. It was concluded that periodontal therapy improved glycemic control in patients with type 2 DM in both groups; however, the use of amoxicillin/clavulanic acid significantly reduced HbA1c values below that achieved by root planning alone.

Schara et al., (2006), evaluated that type 1 diabetes patients with periodontitis will experience improvement in periodontal status and glycemic control after a full full-mouth disinfection treatment. Ten type 1 diabetes patients, between 26-55 years of age and with a mean duration of diabetes of 8.8 years (range 5-15 years) were included in the study. All patients had poor metabolic control with mean glycated hemoglobin (HbA1c) values of 10.5%. All patients received a full-mouth disinfection in 24 hours at baseline and 6 months later. The periodontal parameters

included plaque index (PI), bleeding on probing (BOP), probing depth (PD) and clinical attachment level (CAL). All parameter were recorded at six measuring points (mesiobuccal, buccal, distobuccal, mesiolingual, lingual, and distolingual) on all teeth (excluding 3rd molars) at each of five visits. The clinical parameters and serum level of HbA1c were measured at baseline and at 3, 6, 9 and 12 months. The results demonstrated a significantly lower plaque index, less bleeding on probing, reduction in probing depth and gain of clinical attachment at 3 months and 9 months. Similarly, a significant reduction in the serum level of HbA1c was measured three months after full-mouth disinfection but disappeared 6 months later at the 6 and 12 month recall. It was concluded that a full-mouth disinfection approach significantly improves periodontal status and metabolic control in type 1 diabetes patients with periodontitis.

Patrica A.A et al., (2008), evaluated the effects of periodontal therapy (scaling and rot planning [SRP]) on the serum levels of glycated hemoglobin (HbA1c) and on inflammatory biomarkers. Thirty subjects with type 2 DM and periodontitis were included. Computerized periodontal probe was used for periodontal measurements which were recorded for six sites per tooth at baseline and at 3 months after periodontal treatment. The parameter recorded were PD, relative clinical attachment level (CAL), bleeding on probing (BOP), suppuration (SUP), and the presence and absence of biofilm at four sites per tooth. Inflammatory markers and HbA1c measurements were done with fifteen milliliters of blood obtained by venipuncture from each participant at baseline and at 3 months after therapy. Thirty subjects with type 2 DM and periodontitis were treated with SRP+placebo (SRP; N=15) or with SRP+ doxycycline (SRP+Doxy; N = 15), 100 mg/day, for 14 days. After 3 months, the reduction in probing depth was 0.8 mm for the SRP group and 1.1 mm for the SRP+Doxy group followed by a 0.9% (SRP) and 1.5% (SRP+Doxy) reduction in HbA1c levels. A significant reduction in interleukin (IL)-6; interferon-inducible protein 10; soluble fas ligand; granulocyte colony- stimulating factors; RANTES; and IL-12p 70 serum levels were also verified (N = 30).It was concluded that periodontal therapy may influence the systemic conditions of patients with type 2 DM, but no statistical difference was observed with the adjunctive systemic doxycycline therapy. Moreover, it was possible that the observed improvement in glycemic control and in the reduction of inflammatory markers could be due to diet which was not controlled in the study.

The conflicting data are difficult to interpret, especially given the wide range of medical treatment regimens used by study populations, which may confound

changes related to resolutation of periodontal inflammation (Janket S-J, Wightman A, Baird AE, Van Dyke TE, Jones JA; 2005). In most studies, there is significant variation in glycemic control changes of individual subjects after periodontal therapy. For example, responses can range from major reduction in HbA1c values of 1–2 absolute percentage points or more, whereas in other subjects receiving the same therapy. HbA1c values may change little or may even worsen (Stewart JE, Pager KA, Friedlander AH, Zadeh HH; 2001). A recent meta-analysis of 10 intervention trials included 456 patients (Janket S-J, Wightman A, Baird AE, Van Dyke TE, Jones JA; 2005). After periodontal therapy, the weighted average decrease in absolute HbA1c values was 0.4% but this was not found to be statistically significant. The addition of adjunctive systemic antibiotics to the mechanical therapy regimen resulted in an average absolute reduction of 17%. Again, this reduction did not achieve a level of statistical significance. The auther of this meta-analysis pointed out numerous problem with existing studies with type 1 and type 2 diabetes, and confounding effects of smoking, body mass index, and medications, among others. Further studies are required to determine whether periodontal therapy provides a significant benefit on glycemic control.

Mechanism by Which Periodontal Disease Infection Influence Diabetes

Periodontal disease may induce or perpetuate an elevated systemic chronic inflammatory state (Loos BG;2005). Acute bacterial and viral infection are known to increase insulin resistance in people without diabetes, a condition which often persists for weeks to months after clinical recovery from the illness (Sammalkorpi K; 1989 & Yki-Jarvinen H, Sammalkorpi K, Koivisto VA, Nikkila EA; 1989). Such illnesses and resultant increases in insulin resistance in people with diabetes greatly aggravate glycemic control. Chronic gram negative periodontal infection may also result in increased insulin resistance and poor glycemic control (Genco RJ, Grossi SG, Ho A, Nishimura F, Murayama Y; 2005). Treatment that reduces periodontal inflammation may restore insulin sensitivity, resulting in improved metabolic control. The previously discussed intervention studies that showed improved glycemic control following periodontal therapy support such a hypothesis.

Studies suggest that periodontitis patients, particularly those colonized by Gram-negative organisms such as P. gingivalis, Tannerella forsythensis, and prevotella intermedia, or their products stimulate cells such as fibroblast, Keratinocytes, and macrophages, which are present in periodontal tissue, to release

a number of inflammatory cytokines, such as tumor necrosis factor alpha (TNF-α); prostaglandin E2; interleukin (IL)-1β,-6 (Taba M Jr, Kinney J, Kim AS, Giannobile WV; 2005) and 12 (Fokkema SJ, Loos BG, van der Velden U; 2003) granulocyte colony-stimulating factor (G-CSF); (Sugiyama A, Uehara A, Lki K, et al., 2002) and chemokines, such as IL-8; regulated on activation, normal T-cell expressed, and secreted (RANTES); interferon-inducible protein (IP)-10; and macrophage inflammatory protein (MIP)-1α, that are relevant to inflammatory processes in periodontal diseases (Fokkema SJ, Loos BG, Van Der Velden U;2003, Kabashima H, Yoneda M, Nagata K, Hirofuji T, Maeda K;2002 & Garlet GP, Avila-Campos MJ, Milanezi CM, Ferreira BR, Silva JS;2005). The elevation in cytokine and chemokine expression by cells within the gingival connective tissue in chronic periodontitis lesions may result in increased levels of these mediators in the blood circulation where they can induce or perpetuate systemic effects (Graves DT, Liu R, Alikhani M, AL-Mashat H, Trackman PC;2006).

The elevated serum levels of these important mediators have deleterious effects on glucose and lipid metabolism (D'Aiuto F, Nibali L, Parkar M, Suvan J, Tonetti MS;2005). TNF-α was reported to interfere with lipid metabolism. TNF-α can induce insulin resistance at the receptor level by preventing autophosphorylation of the insulin receptor and suppressing second messenger signaling through the inhibition of the enzyme tyrosine kinase (Fernandez-Real JM, Ricart W; 2003). Infusion of TNF-α in healthy humans directly induces resistance in skeletal muscle and reduces glucose uptake and use (Plomgaard P, Bouzakri K, Krogh-Madsen R, Mitter Dorfer B, Zierath JR, Pedersen BK;2005). Blocking TNF-α with pharmacologic agents has been shown to reduce serum insulin levels and improve insulin sensitivity in some subjects (Gonzalez – Gay MA, DeMatias JM, Gonzalez-Juanatez C et al., 2006) but not in others (Dominguez H, Storgaard H, Rask-Madsen C et al., 2005). IL-6 stimulates TNF-α production; therefore, increased production of IL-6 causes elevated TNF-α production, which may further exacerbate insulin resistance. IL-6 and 1 receptor antagonist (ra) were also reported to antagonize insulin action. The increased production of TNF-α and IL-6 also stimulates greater hepatic CRP production, which may also increase insulin resistance (Festa A, D'Agostino R Jr, Howard G, Mykkanen L, Tracy RP, Haffner SM;2002 & Natali A, Toschi E, Baldeweg S, et al., 2006). Furthermore, it was shown that diabetes up regulates the production of inflammatory cytokine and chemokines (Esposito K, Nappo F, Marfella R, et al., 2002), leading to increased inflammation, tissue damage, and apoptosis in patients who have periodontitis (Mealey BL, Oates TW; 2006, Graves DT, Liu R, Alikhani M, Al-Mashat H, Trackman PC; 2006 & Gamonal J, Bascones A, Acevedo A, Blanco E, Silva A; 2001).

Multiple mechanisms are involved in regulation of insulin sensitivity and resistance, including adipokines, genetic factors, environmental stresses, and inflammatory mediators. As an inflammatory condition, periodontal diseases may also play a role in these processes. In addition to the elevated systemic inflammatory state associated with periodontitis people with diabetes often have a shift in monocyte/macrophage phenotype, which results in the overproduction of these same inflammatory cytokines in response to periodontal pathogens (Salvi GE, Collins JG, Yalda B, Arnold RR, Lang NP, Offenbacher S;1997). Diabetic patients who also have periodontitis may present with an even greater systemic inflammatory condition with elevated serum level of IL-6, TNF-α, and CRP, which can worsen insulin resistance and thereby aggravate glycemic control. This could explain why periodontitis increases the risk of poor glycemic control in patients with type 2 diabetes (Taylor GW, Burt BA, Becker MP, et al., 1996). It may also explain why improvement in glycemic control has followed periodontal therapy in some studies of diabetes subjects (Miller LS, Manwell MA, Newbold D, et al., 1992, Grossi SG, Skrepcinski FB, De Caro T, et al., 1997, Stewart JE, Pager KA, Friedlander AH, Zadeh HH; 2001 & Kiran M, Arpak N, Unsal E, Erdogan Mf; 2005). In a small study of 13 type 2 diabetic subjects with periodontitis, periodontal treatment consisting of mechanical debridement and local delivery of minocycline resulted in a significant reduction in serum TNF-α levels that was accompanied by a significant reduction in mean HbA1c levels from 8.0–7.1% (Iwamoto Y, Nishimura F, Nakagawa M et al., 2005). Reductions in HbA1c values were strongly correlated with the reduction in serum TNF-α levels across the patient population. Thus, periodontal treatment may reduce inflammation locally and also decrease serum levels of the inflammatory mediators that cause insulin resistance, thereby positively affecting glycemic control.

Periodontal diseases and diabetes mellitus are closely associated and are highly prevalent chronic disease with many similarities pathbilogy. Insulin resistance may play an important role in this relationship. Inflammation is a critical player in the association, and its importance is just now coming to light. Till date the impact of periodontal diseases on glycemic control of diabetes and the mechanisms through which this occurs is not clear. It is possible that periodontal diseases may serve as initiators or propagators of insulin resistance, thereby aggravating glycemic control. Further research is needed to clarify this aspect of the relationship between periodontal diseases and diabetes.

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CHAPTER 4

Effect of Periodontal Disease on Chronic Obstructive Pulmonary Disease

Recent studies have provided provocative evidence for a role of periodontal infections in the initiation and/or progression of several important systemic diseases. Epidemiological reports have implicated periodontal disease as a potential risk factor for chronic obstructive pulmonary disease (COPD) and pneumonia (Garcia et al, 2001). COPD, characterized by chronic blockage in the airflow and breathing-related problems, includes two lung diseases, chronic bronchitis and emphysema, and sometimes asthma.

The main risk factor for COPD is smoking, air pollution, second hand smoke, history of childhood respiratory infections, genetic factors, and heredity are among other risk factors for COPD (American lung association; 2005). One of the major complications of COPD is the occurrence of "exacerbations", or episodes in which there are objective signs that bronchitis has worsened as evidenced by increased sputum production showing a change in color and/or consistency. Increased cough, dyspnea, chest tightness and fatigue may also accompany an exacerbation. However, the factors responsible for the initiation of exacerbation are not completely known, although they are thought to be provoked in part by bacterial infection (Murphy et al., 1992, Fagon et al., 1992). The organisms most closely associated with exacerbations are non-typeable H. Influenzae, S. Pneumoniae and M. Catarrhalis.

Pneumonia, an acute condition, manifests as the "gradual onset of cough with little or no fever. Less common presentations are pharyngitis, laryngitis, and sinusitis. The spectrum of illness can range from asymptomatic infection to severe disease. Bacterial Pneumonia can be divided into community acquired or hospital acquired types depending upon the etiologic agent responsible.

Community acquired pneumonia is typically caused by pathogens that normally reside on the oropharyngeal mucosa, such as Streptococcus Pneumonia, Haemophilus Influenzae, Mycoplasma Pneumonia. In contrast, hospital acquired,

or nosocomial, pneumonia is often caused by bacteria that are not normally residents of the oropharynx but that enter this milieu from the environment, including Gram-negative bacilli, Pseudomonas, aeruginosa, and Staphylococcus aureus.

The factors responsible for the initiation of pulmonary disease and the occurrence of exacerbations are not completely known, although they are thought to be provoked in part by bacterial infection (Murphy et al.,1992, Fagon et al., 1996). It is therefore possible that accumulation of oral pathogens associated with periodontal disease may increase the risk for serious lower respiratory tract infection in susceptible subjects, including pneumonia in hospitalized subjects or exacerbation and progression of COPD. Periodontal disease may alter environmental condition to permit mucosal colonization and infection by respiratory pathogens (Scannapieco et al., 1996, Fourier et al., 1998, Hayes et al., 1998). Oral conditions likely work in concert with other factors (continued smoking, environmental pollutants, viral infections, allergy, genetic factors, etc.) to contribute to progression of respiratory diseases.

Epidemiological Studies

Scanapieco et al., (1998), assessed potential association between respiratory disease and oral health status by analyzing data from the national health and nutrition survey of 23,808 individuals. Of these, 386 individuals reported a suspected respiratory condition were categorized as having a confirmed chronic respiratory disease (chronic bronchitis or emphysema) or an acute respiratory disease (influenza, pneumonia, acute bronchitis). They were compared to those not having a respiratory disease. More subjects with chronic respiratory disease were male, and a significantly greater proportion of the subjects with acute disease were smokers. Individuals with a confirmed chronic respiratory disease (n=4) had a significantly greater oral hygiene index than subjects without a respiratory disease (n=193). After controlling for smoking, non-smokers with chronic disease appeared to have poorer oral hygiene than those with no chronic disease. Non-smokers with chronic diseases (n=17) were found to have more calculus, worse oral hygiene, fewer permanent teeth per mouth (P=O-013), and more decayed teeth than non-smokers without chronic disease (n=124). No associations were noted between the periodontal index and either acute or chronic disease. There were proportionally more males with chronic disease than without as well as smokers with acute disease than without, while the disease groups were balanced with respect to age and race. However, age, gender, and smoking status were all

associated in the study group. These results suggested that OHI to have a residual effect on chronic respiratory disease of both practical and statistical significance.

Treloar et. a1(1995), provided an oral examination (at entry to the study and every other day thereafter), plaque index, gingival index, and oropharyngeal cultures for 16 intubated patients admitted to a medical ICU. No control subjects were assessed. Pneumonia was diagnosed by quantitation of pathogenic bacteria in tracheobronchial secretions, and new infiltrates on chest radiographs. While 7 of 16 subjects (44%) demonstrated pneumonia associated x-ray changes. It was concluded that no clear relationship was noted between oral conditions and pneumonia diagnosis.

Fourier et al,. (1998), studied the association of oral health status including dental caries, dental plaque, and colonization of dental plaque by respiratory pathogens, and onset of pneumonia in 57 ICU patients. They reported that the relative risk for pneumonia was increased 9.6 fold when dental plaque was colonized by a pathogens between days 0 and 5 following ICU admission. It was concluded that the pathogen causing pneumonia first colonized the dental plaque.

Terpenning et al., (1993), assessed 134 geriatric patients (34 inpatients, 53 long-term care patients, and 47 outpatients). They assessed oral conditions such as xerostomia, caries, periodontal disease, and salivary IgA levels. These were compared to diagnosis of aspiration pneumonia based upon body temperature >2c above baseline, clinical deterioration, elevated white blood cell count, and infiltrates on chest radiograph. It was concluded that 27% of dentate inpatients and 19% of dentate long-term care patients developed aspiration pneumonia, while only 5% of the edentulous patients developed pneumonia.

Mojan et al., (1997), assessed the relationship of oral health status and lung infection in 302 nursing home residents. They found an increased risk for respiratory tract infection in subjects with teeth in comparison to edentulous subjects.

Preston et al., (1999), found the dental plaque of 12 of 28 (43%) elderly patients recently admitted to a hospital were colonized by gram-negative bacillary pathogens, which suggested the possibility that dental plaque may serve as a reservoir for lung infections.

Russell et al., (2001), compared 28 chronic care nursing home residents with 30 dental clinic outpatients over 65 years of age, matched for gender and race. They found that the dental plaque scores were significantly higher in the nursing

home residents than in the outpatient controls. It was concluded that 14.3% of chronic care subjects showed dental plaque colonization with respiratory pathogens compared to none of the control outpatients.

Hayes et al., (1998), investigated whether the risk for chronic obstructive pulmonary disease (COPD) was enhanced among individuals with moderate to severe periodontal disease as assessed' by radiographic alveolar bone 10ss (ABL). Those Subjects with a forced expiratory volume in 1 second (FEV1) less than 65% of predicted volume were categorized as having COPD. ABL was assessed by using full mouth series periapical films measured by a Schei ruler. Bone loss at each interproximal site was measured in 20% increments, and the mean whole-mouth bone loss score was calculated. A logistic regression model was estimated to assess the independent contribution of ABL status at baseline, when all men were medically healthy and free of COPD, to their risk of subsequently developing COPD over a 25 year follow-up period. Important cofactors included measure of age, education, smoking, alcohol consumption, and height. The relative risks, as estimated by odds ratio, were calculated from the parameter estimates of logistic regression models. Of the 1,118 medically healthy dentate men at baseline, 261 subsequently developed COPD. It was found that ABL status at baseline was an independent risk factor for COPD, with subjects in the worst population quintile of bone loss (mean ABL > 20% per site) found to be at significantly higher risk (OR = 1.8, CI = 1.3, 2.5). The results indicated that periodontal status, as assessed by radiographic measures of alveolar bone loss, was associated with an increased risk for COPD in this longitudinal study.

Scannapieco FA et al., (1998), assessed the association between COPD and oral health in community-dwelling populations of 23,808 individuals. Of these, 365 individuals reported a respiratory condition. These subjects were categorized as having a confirmed chronic respiratory disease (chronic bronchitis, emphysema), acute respiratory disease (influenza, pneumonia, acute bronchitis), or not having a respiratory disease. It was concluded that poor oral hygiene and smoking status were statistically associated with chronic respiratory disease.

Scannapieco FA et al., (2001), verified the results which documented the general health and nutritional status of randomly selected subjects from 1998 to 1994. The study included 13,792 subjects $\geq$ 20 years of age having at least 6 natural teeth. Subjects with a history of bronchitis and/or emphysema were considered as having COPD. Subjects with COPD had on average, more clinical

attachment loss (CAL 1.48 mm) than those without COPD (mean CAL 1.17 mm). To simultaneously control for multiple variables that may confound statistical analysis, gender, age, race, education, income, dental treatment history, alcohol consumption, diabetes status, and smoking status were considered in a logistic regression model against history of COPD. A trend was noted in that lung function appeared to diminish as the amount of attachment loss increased. It was concluded that oral disease such as periodontitis may be associated with COPD.

Garcia et al., (2001), examined the risk of developing COPD assessed by spirometry in 1,112 subjects, 279 of whom developed COPD. They found that subjects in the quintile having the worst periodontal health at baseline (measured by radiographic bone loss or probing depth) had greater risk for developing COPD when compared to all other subjects, after controlling for smoking. It was concluded that worse periodontal status increased the risk for COPD in current smokers, but not in never smokers.

Poor oral health, characterized by inadequate hygiene resulting in the formation of extensive dental biofilms (plaque) may promote oral colonization of respiratory pathogens. Poor oral health may also influence the quality of respiratory epithelium resulting in increased susceptibility to respiratory infection. Oral secretions and/or oral bacteria may contain hydrolytic enzymes or cytokines that alter epithelial surfaces in ways that increase susceptibility to adhesion and colonization by respiratory pathogens. Thus, poor oral health may increase the risk for serious lower respiratory tract infection in susceptible subjects, including pneumonia in hospitalized subjects or exacerbation and progression of COPD.

It is possible that the teeth and periodontium can serve as a reservoir for respiratory infection. Oral bacteria can be released from the dental plaque into the salivary secretions which are then aspirated into the lower respiratory tract to cause pneumonia. It has been long known that severe anaerobic lung infections can occur following aspiration of salivary secretions, especially in patients with periodontal disease.

However, there is as yet no direct evidence for a causal relationship between periodontal diseases and respiratory diseases. While plausible biological mechanisms have been proposed to explain the reported epidemiologic associations, causality may not yet be inferred. In contrast, there is extensive evidence available indicating that a greater burden of oral infection (e.g, as indicated by plaque accumulation) in a particularly susceptible host (e.g, medically-compromised elders, ICU patients) may

increase the risk for certain community-acquired or nosocomial pneumonias and for exacerbations of COPD. Simply stated, it may be hypothesized that "teeth may serve as a reservoir for respiratory infection" (Scannapieco et al., 1999). Such oral-systemic association may best be investigated through controlled intervention studies. There now exists sufficient evidence to justify undertaking such definite trials.

Oral Intervention Trials

The findings reviewed for epidemiological studies suggest that the oral cavity may serve as a reservoir for lower airway infection, especially in institutionalized subjects. This observation further suggests that improved oral hygiene could reduce or eliminate respiratory pathogens from the mouth and thus prevent the onset of serious respiratory infection in vulnerable subjects. Although oral hygiene measures are a component of nursing care, implementation of such measures is difficult in some patients, such as those who are orally intubated. Oral interventions to reduce pulmonary infections have been examined in both mechanically ventilated ICU patients and non-ventilated elderly patients. These studies included chemical intervention using topical antimicrobial agents and traditional oral mechanical hygiene performed by a professional.

The first study to assess an oral intervention in the prevention of respiratory infection was reported by Kuriakona in 1977. A group of 295 children (173 experimental and 123 control) with chronic pneumonia were assessed. Respiratory symptoms and the incidence of cold, influenza, and active periods of chronic pulmonary disease were assessed over a 1 year period. The test group received "systematic sanitation" (regular cleaning) of the oral cavity, while the control group received normal oral hygiene (no clear description of the oral cleaning methods were provided). It was concluded that children whose oral cavities were systematically sanitized experienced active periods of chronic pneumonia 1.7 times less frequently than children in the control group.

Pugin et al., (1991), studied 52 ICU patients; 25 in a test group received topical non absorbable PNV solution (150 mg of polymxin B sulfate, 1 g of neomycin sulfate, 1 g of vancomycin hydrochloride in 60 ml of 5% dextrose) and 27 in a placebo group received topical 5% dextrose. Both treatment were applied to the retropharynx every 24 hours and then swallowed. It was concluded that antibiotic solutions reduced tracheobronchial colonization by gram-negative respiratory pathogens and S. SAureus, and the rate of pneumonia by a factor of 5 when compared to the control treatment.

DeRiso et al., (1996), compared the effectiveness of oral topical chlorhexidine gluconate (CHX) to reduce pneumonia was examined in patients placed on mechanical ventilation after cardiac surgery. Patients were randomly assigned to receive either 0.12% CHX (treatment) or vehicle alone (placebo), applied twice daily to buccal, pharyngeal, gingival, tongue, and tooth surfaces. Exposure to topical CHX reduced the incidence of total respiratory tract infections in the CHX group by 69%. It was concluded that intervention significantly reduced total mortality (1.16% versus 5.56%), and the need for systemic antibiotics.

Fourier et al., (2000), trialed chlorhexidine intervention of 160 ICU patients requiring mechanical ventilation. A test group of 30 patients received 0.2% CHX gel 3 times a day. The control group received an oral rinse with bicarbonate isotonic serum and oropharyngeal aspiration 4 times a day. It was concluded that oral antiseptic decontamination with CHX gel significantly reduced the incidence of nosocomial pneumonia.

Genuit et al., (2001), reported 95 surgical ICU patients who received 0.12% chlorhexidine oral rinse 2 times a day with ventilator weaning protocol (WP). A "placebo control" received only the WP. Rates of pneumonia were compared to 39 historic controls from hospital databases. WP plus CHX oral rinse showed significant reduction and delay of occurrence of pneumonia when compared to the historic controls and those who received the WP alone.

Bergmans et al., (2001), evaluated 3 groups of patients admitted to 3 ICUs over a 2 year period. The test group of 87 patients received pain reliever with 2% gentamicin/colistin/vancomycin every 6 hours. A placebo group of 78 patients received the pain reliever without antibiotics. A control group of 61 patients received no treatment. It was concluded that the topical antibiotic treatment prevented acquired oropharyngeal colonization (10% vs 59% placebo and 63% control) and the incidence of pneumonia (10% versus 31% in placebo and 23% in the control group.

Yoneyama et al., (1996), found in 46 elderly nursing-home patients that professional dental care once a day (supervised tooth brushing, plus oral topical 1% povidine iodine) reduced the number of febrile days in a limited number of patients. This study was followed up with a second study in which 366 elderly residents from 11 nursing-homes were enrolled. A test group of 184 subjects received supervised tooth brushing after each meal, and topical 1% povidone iodine once a day. A control group of 182 subjects received no intervention. A

2-year follow-up found that the relative risk of pneumonia in the group with no active oral care was 67% greater when compared to the oral group.

Oral colonization by respiratory pathogens appears to be a risk factor for lung infection in high risk subjects. Several rather small-scale interventional trials suggest that improved oral care may reduce the incidence of nosocomial pneumonia. Additional multicenter trials will determine the generating ability of oral intervention in the prevention of pneumonia in the institutional setting. Such studies must monitor appropriate aspects of normal health status to draw proper conclusions regarding the role of oral health in the prevention of pneumonia. Additional longitudinal epidemiologic studies are required to validate the reported association between periodontal disease and COPD. Randomized controlled intervention studies that test the effect of periodontal treatment on the progression of COPD are needed.

Role of Oral Bacteria in Respiratory Infection

Several respiratory diseases, including bacterial pneumonia and chronic obstructive pulmonary disease (COPD), have also been associated with periodontal disease. The microbiology of pneumonia differs depending on the population affected. Community- acquired pneumonia is typically caused by pathogens that normally reside on the oropharyngeal mucosa, such as streoptococcus pneumonia, Haemophilus influenza, Mycoplasma pneumonia, Chalmydia pneumonia, Legionella pneumophila, Candida albicans, and anaerobic species. In distinction, hospital acquired, pneumonia is often caused by bacteria that are not normally residants of the oropharynx but that enter this milieu from the environment, including Gram negative bacilli (enterics such as Escherichia Coli, Klebsiella pneumonia, Serratia spps, Enterbacter spps.), Pseudomonas aeruginosa and Staphylococcus aureus. Another severe respiratory disease affecting a significant segment of the population is COPD. This condition is characterized by chronic obstruction to airflow with excess production of sputum resulting from chronic bronchitis (CB) and or emphysema (Ingram et al., 1994). One of the major complications of COPD is the occurrence of “exacerbations,” or episodes in which there are objective signs that bronchitis has worsened as evidenced by increased sputum production, increased cough, dyspnea, chest tightness, fatigue may also accompany an exacerbation. However, the factors responsible for the initiation of exacerbation are not completely known, although they are thought to be provoked in part by bacterial infection (Murphy et al., 1992, Fagon et al.,

1996). The organisms most closely associated with exacerbation are non-typeable H. Influenzae, S. Pneumonia and M. Catarrhalis.

Lower respiratory infection begins by contamination of the lower airway epithelium by micro-organisms contained in aerosolized droplets or by aspiration of oral secretions containing microorganisms. A critical step in this process is thus the colonization of oropharyngeal mucosal surfaces by respiratory pathogens and the shedding of attached bacteria from these surfaces into contiguous secretions that subsequently contaminate the lower respiratory tree (Johanson et al., 1969, Donowitz et al., 1990, Finegold et al., 1991). Recent evidence now supports the oropharyngeal region as the likely source of the bacteria (Garrouste et al., 1997). Failure of host defense mechanisms to eliminate these pathogens from the lower respiratory surfaces results in their multiplication with subsequent infection and tissue destruction (Estes et al., 1995, Toews et al., 1986, Bentluey et al., 1984). It is therefore possible that lower respiratory infection may be prevented by suppressing initial oropharyngeal respiratory pathogen colonization.

Fourrier et al., (1998), stated that the potential respiratory pathogens were prevalent and abundant on the teeth and/ or buccal mucosa of the intensive care unit patients, 65% of whom were colonized at these sites compared with only 16% of ambulatory dental patients colonized at the same sites ($P < 0.005$). The potential respiratory pathogens identified in the oral flora of intensive care unit patients included S. Aureus, Pseudomonas aeruginosa, and a number of enteric species. Several patients had oropharyngeal colonization by two or more potential pathogens, and in some cases the pathogen comprised up to 100% of the culturable aerobic flora. A number of studies have verified that the teeth and other oral surfaces of intensive care unit subjects serve as reservoirs of respiratory pathogen colonization. It has been reported that the relative risk for pneumonia is increased by 9.6 fold when the dental plaque is colonized by a potential respiratory pathogen between days 0 and 5 following intensive care unit admission. In some cases, the pathogen causing pneumonia appeared to first colonize the dental plaque.

A recent study by Didilescu et al., (2005), assessed dental plaque as a reservoir of respiratory pathogen colonization in hospitalized patients with chronic lung diseases using a checkerboard DNA-DNA hybridization technique to determine the prevalence of eight respiratory pathogens and eight oral pathogens, species such as *S. Aureus, P. Aeruginosa, Acinetobacter Baumannii,* and *Enterobacter Cloacae* were detected in dental plaque from 29 of the 34 (85.3%) hospitalized

patients, whereas only 12 of 31 (38.7%) nonhospitalized subjects were colonized. These results indicate that dental plaque may serve as a reservoir of infection in hospital patients with chronic lung diseases. Evidence has also been presented that demonstrates the genetic identity of respiratory pathogen isolates recovered from the bronchoalveolar lavage fluid of hospitalized institutionalized elderly individuals and isolates from the dental plaques of the same patients (Pietrantoni et al., 2004). These results confirm that dental plaque serves as an important reservoir of respiratory pathogens in this patient cohort.

It has become apparent in recent years that the oral cavity may be an important reservoir for bacterial pathogens that cause lung disease. The incidence of respiratory pathogen oropharyngeal colonization by respiratory pathogens appears to be more common in patients with teeth or dentures than in edentulous patients who do not wear dentures (Terpenning et al., 1993). Diminished salivation and salivary pH may promote colonization by respiratory pathogens, these conditions occur in ill patients and in those receiving various medications (Terpenning et al., 1993). Oral colonization by respiratory pathogens is common in institutionalized patients, especially those admitted to hospital ICUs and in the elderly who are debilitated, hospitalized, or in a nursing home (Scannapieco et al., 1996, Limeback et al., 1998, Russell et al., 1999). Poor oral hygiene and periodontal disease may foster respiratory pathogen oropharyngeal colonization, and patients who are hospitalized or reside in a nursing home often have poorer oral hygiene than community-dwelling individuals (Russell et al., 1999).

Several mechanisms can be envisioned to help explain how oral bacteria can participate in the pathogenesis of respiratory infection: 1) aspiration of oral pathogens (such as *P. Gingivalis,* A. *Actinomycetemcomitans,* etc.) into the lung; 2) periodontal disease-associated enzymes in saliva may modify mucosal surfaces to promote adhesion and colonization by respiratory pathogens; 3) periodontal disease-associated enzymes may destroy salivary pellicles on pathogenic bacteria; and 4) cytokines originating from periodontal tissues may alter respiratory epithelium to promote infection by respiratory pathogens.

a) Aspiration of Oral Pathogens into the Lungs

It is possible that the teeth and periodontium can serve as a reservoir for respiratory infection. Oral bacteria can be released from the dental plaque into the salivary secretions which are then aspirated into the lower respiratory tract to cause pneumonia. Indeed, it has been long known that severe anaerobic lung infections

can occur following aspiration of salivary secretions, especially in patients with periodontal disease (Donowitz et al., 1990, Finegold et al., 1991, Sinclair et al., 1994). Estimates have been made that 30–40% of all cases of aspiration pneumonia, necrotizing pneumonia, or lung abscess involve anaerobic bacteria (Brook et al., 1993). A variety of oral anaerobes and facultative species have been cultured from infected lung fluids, including Porphyromonas gingivalis, Bacteroides gracilus, Bacteroides oralis, Bacteroides buccae, Eikenella corrodens, Fusobacterium nucleatum, Fusobacterium necrophorum, Actinobacillus actinomycetecomitans, Peptostreptococci, Clostridium and Actinomyces (Brook et al., 1993, Goldstein et al., 1979, Yuan et al., 1994). Most if not all of these organisms have been associated with periodontal disease (Moore et al., 1994, Slots et al., 1992). It is also possible that viridians streptococci, thought to be exclusively benign members of the oral flora, may participate in the initiation and/or progression of pneumonia (Mahomed et al., 1992, Appelbaum et al., 1978). Oral bacteria may also have a role in the exacerbations of COPD. For example, viridans streptococci were found to be the cause of pneumonia in 4% of COPD patients (Torres et al., 1996). Laboratory studies also suggest that oral anaerobes such as *P. Gingivalis* can cause marked inflammation when instilled into the lungs of laboratory animals (Nelson et al., 1986). A relationship between the systemic humoral response to *Prevotlla* species (bacteria associated with periodontal disease) and ventilator-associated pneumonia in hospitalized patients has also been described. Thus, colonization of patients by *Preuotella* species may be associated with an infectious process leading to ventilator-associated pneumonia and a systemic humoral response (Grollier et al., 1996).

b) Periodontal Disease-Associated Enzymes in Saliva May Modify Mucosal surfaces

Previous studies have shown that respiratory pathogens such as *P. Aeruginosa* may adhere better to oral epithelial cells obtained from patients colonized by respiratory pathogens than to cells harvested from non-colonized patients (Langmore et al., 1998, Johanson et al., 1980). Trypsin treatment of epithelial cells from non-colonized patients in vitro resulted in increased adhesion by respiratory pathogens. These data suggest a mucosal alteration, perhaps the loss of fibronectin from the epithelial cell surface, promoted bacterial adhesion (Woods et al., 1981). Buccal epithelial cells from gravely ill patients, all colonized by *P. Aeruginosa*, interacted with greater numbers of bacterial cells in vitro, and possessed lesser amounts of surface fibronectin as determined by immunofluorescence. The removal of

fibronectin (by exposure to proteases) may unmask mucosal surface receptors for respiratory pathogen adhesins. Other investigators have also pointed out an inverse relation between the amount of mucosal epithelial' cell fibronectin and Gram-negative bacilli binding to these cell (Abraham et al., 1983).

Saliva contains a wide assortment of hydrolytic enzymes, and the amount of enzyme activity in saliva is related to the periodontal and oral hygiene status of the subjects tested (Nakamura et al., 1983, Gibbons et al.,.1986). For example, a direct relationship has been found between the ability of saliva to degrade fibronectin and oral hygiene status (Gibbons et al., 1986). Subjects practicing meticulous oral hygiene (dental hygiene students) had very low levels of salivary fibronectin degrading enzymes. In contrast, saliva samples collected from laboratory workers having less than ideal oral hygiene had higher amounts of enzyme activity, and saliva collected upon awakening in the latter group had even higher levels. The source of these enzymes has been attributed to bacteria (Nakamura et al., 1983, Zambon et al., 1985, Frandsen et al., 1987) or polymorphonuclear leukocytes which enter saliva from the gingival sulcus (Benedek et al., 1991). It is conceivable that in subjects having periodontal disease and elevated levels of proteolytic bacteria such as *P. Gingiva Lis* and spirochetes, protease activity may alter the mucosal epithelium to increase the adhesion and colonization of respiratory pathogens. Such bacteria may also produce other enzymes such as mannosidase, fucosidase, hexosaminidase, and sialidase, known to be elevated in the saliva of such patients (Quinn et al., 1994, Weinmeister et al., 1994). Exposure of epithelium and glycoproteins by such enzymes may increase the adhesion of Gram-negative bacteria to the mucosal surface by exposing normally "buried" adhesion receptors on the mucosal epithelium (Gibbons et al., 1990) which may foster increased adhesion and colonization by respiratory pathogens.

c) Destruction of Protective Salivary Pellicles by Oral Bacteria

Recent evidence suggests that the respiratory pathogen *H. Influenzae* binds to mucins contained within mucosal secretions (Reddy et al., 1997). This binding may involve sialic acid residues (Reddy et al., 1997). In the context of COPD, it is possible that subjects with poor oral hygiene may have elevated levels of hydrolytic enzymes (e.g. sialidase) in their saliva. These enzymes may process mucins which reduce their ability to bind to and clear pathogens such as *H. Influenzae.* Conversely, enzymes may process the respiratory epithelium to modulate adhesion of such pathogens in the mucosal surface. Indeed, several studies have suggested that certain oral bacteria can breakdown a variety of salivary components (Scannapieco

et al., 1994). Thus increased dental plaque load from poor oral hygiene may result in elevated levels of salivary hydrolytic enzymes, which in turn may destroy protective domains of host secretory components (e.g. mucin) thus diminishing non-specific host defense against respiratory pathogens in high-risk subjects.

d) Salivary Cytokines May Alter Respiratory Epithelium

Periodontal disease (periodontitis) is a localized chronic inflammatory disease caused by infection of the periodontal tissues by bacteria in dental plaque resulting in destruction of supporting bone and connective tissues. In untreated periodontal disease, oral pathogens continuously stimulate cells of the oral tissues and periodontium (epithelial cells, endothelial cells, fibroblasts, macrophages, white cells) to reduce a wide variety of cytokines and other biologically active molecules (Reddi et al., 1996). Cytokines produced by, epithelial and connective tissue cells in response to these bacteria including IL-lα, IL-1β, IL-6, IL-8,and TNF. Oral bacteria can also stimulate peripheral mononuclear cells to release cytokines (IL-lα and TNFα. Infact, oral streptococci (for example *Streptococcus Sanguis),* which are abundant in dental plaque, stimulate the release of high levels of these cytokine from such cells (Kjeldsen et al., 1995). Epithelial cells are also known to alter expression of various cell adhesion molecule on their surface in response to cytokine stimulation.Variation in expression of such adhesion molecule may alter the interaction of bacterial pathogens with the mucosal surface (Khair et al., 1996).

One mechanism proposed for the gross airway epithelial damage observed in COPD involves release of proinflammatory cytokines (i.e., IL-8) from the respiratory epithelium, resulting in the recruitment and infiltration by neutrophils which subsequently release proteolytic enzymes and toxic oxygen radicals. The release of cytokines from the respiratory epithelium may be the result of the binding of pathogens or their products to the respiratory epithelial cells. This mechanism has been demonstrated to medical pathogens such as *Strepto-coccus Pneumniae* and *Haemophilus Influenzae,* which are also known to attach to mucosal receptors and to stimulate cytokine production by the underlying cells (Hakansson et al., 1996). It is also conceivable that oral bacteria in secretions in contact with respiratory epithelial surfaces may adhere to the mucosal, surface. Oral bacteria are routinely cultivated, for example, from tonsillar epithelium (Brook et al., 1995). These bound oral bacteria may stimulate cytokine production by mucosal epithelium. It is also possible that cytokines originating from the oral tissues (for example from the gingival crevicular fIuids (Rossomando et al., 1993). Which exit the gingival sulcus to be mixed with whole saliva), may contaminate the distal

respiratory epithelium to stimulate respiratory epithelial cells. The stimulated respiratory cells may then release other cytokines that recruit inflammatory cells (e.g" neutrophils) to the site. These inflammatory cells may release hydrolytic enzymes and other modifying molecules resulting in damaged epithelium that may be more susceptible to colonization by respiratory pathogens.

Oral bacteria may influence cytokine expression and effects in more novel ways. A recent paper by Darveau et al., showed that IL-8 is secreted by gingival epithelial cells in response to components of the normal oral flora. In contrast, P. *Gingiualis* strongly inhibited IL-8 accumulation from gingival epithelial cells. Inhibition was associated with a decrease in mRNA for IL-8. Antagonism of IL-8 accumulation did not occur in KB cells, an epithelial cell line that does not support high levels *of* intracellular invasion by P. *Gingiualis.* Furthermore, a noninvasive mutant *of P. Gingiualis* was unable to antagonize IL-8 accumulation. The authors concluded that invasion-dependent destruction *of* the gingival IL-8 chemokine gradient at sites *of P. Gingiualis* colonization may impair mucosal defense. It is not yet known if P. gingiualis would have a similar effect on respiratory epithelium. Such an effect might result in perturbation *of* local cytokine networks and thus promote a destructive inflammatory lesion within the lung.

Poor oral health, characterized by inadequate hygiene resulting in the formation of extensive dental biofilms (plaque) may promote oral colonization of respiratory pathogens. Oral bacteria may modulate the adhesion of respiratory pathogens to epithelial cell lines. Furthermore, both oral and respiratory bacteria appear to induce the release of proinflammatory cytokines from oral and respiratory epithelial cell lines in vitro. Extrapolating this work in vivo, the release of cytokines from mucosal surfaces in response to oral bacterial interactions may change the local microenvironment, and promote the adhesion of microbes to both oral and respiratory epithelial cells, which may facilitate the onset and/or progression of respiratory diseases in susceptible individuals. It is possible that factors responsible for poor oral health may be a determining factor influencing the frequency of respiratory infection in high risk groups. Further research defining the factors responsible for initiating the process of infection, the underlying conditions that may modulate the progression of the disease, and methods to improve its management are clearly needed. It is conceivable that improved oral health may decrease the prevalence of oropharyngeal colonization by respiratory pathogens and thereby reduce the risk of infection in high risk subjects.

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CHAPTER 5

Effect of Periodontal Disease on Cardiovascular Disease

There is increasing evidence that periodontal diseases are associated with increased risk of cardiovascular disease. Different studies have provided evidence of association between poor dental health and acute myocardial infarction (Mattila et al., 1989 & Mattila, 1993) and between dental infection and coronary atherosclerosis in men (Mattila et al.,1993). Subsequently, epidemiological studies from the united states reported that, after adjustment for known cardiovascular risk factor, have shown increased risk of CHD between 50% and 70% in men with periodontitis (De Stefano et al., 1993 & Beck et al., 1996). Recent work from various developed countries have a1lso provided further support for this concept (Persson et al., 2003 & Montebugnoli et al., 2004).

Cardiovascular and periodontal diseases are common inflammatory conditions in the human population. Cardiovascular disease accounts for 29% of deaths worldwide. Atherosclerosis, which is a major component of cardiovascular disease, in which large to medium-sized muscular and large elastic arteries become occluded with fibro-lipid lesions called atheromas. End-stage complications or events associated with atherosclerosis include coronary thrombosis, acute myocardial infarction, and stroke. Traditional risk factors related to behaviors, diet, lifestyle, and family history do not appear to fully account for the development of atherosclerosis. Furthermore, despite continued preventive efforts addressing modifiable risk factors, mortality rates from cardiovascular disease have remained virtually unchanged over the past decade in developed countries.

Clinicians and investigators currently appreciate that inflammation appeals to play a pivotal role in the development of atherosclerosis. This appreciation has intensified the search for chronic exposures or infections that potentially cause inflammation in vessels. Recent observational studies and meta-analyses continue to demonstrate a modest but statistically significant increased risk for cardiovascular disease among persons exposed to periodontal disease or infection.

Experiments with animal models further indicate that periodontal infection can increase atherosclerosis in the presence or absence of hypercholesterolemia. This review will present the latest relevant clinical research data implicating a relationship between cardiovascular and periodontal diseases.

Epidemiological Studies

Mattila et al., (1989) conducted case control study on 100 patients with acute myocardial infarction and 102 controls selected from the community at random. Patients in the first series were 40 consecutive men aged 50 or younger, who were admitted because of acute myocardial infarction. The controls were age, sex, and neighborhood-matched from the community and invited for examination, when the patient was admitted. The second series consisted of 60 consecutive cases: either men aged 60 or younger or women aged 65 or younger. The dental examination was performed, while patients were in the hospital or shortly thereafter. The dental index, which was used in all of the Mattila reports, is the sum of scores for the number of carious lesions, missing teeth, periapical lesions, probing depth measures (including pus in the pocket) and the presence or absence of pericoronitis. These index scores showed that patients had worse dental health than controls in both studies. Logistic regression analysis indicated that the association between poor dental health and coronary heart disease (CHD) was independent of age, total cholesterol, high-density lipoprotein (HDL), triglycerides, C peptide, hypertension, diabetes, and smoking.

Mattila et al., (1993), reported on possible association between dental infections and atherosclerosis from a case-control study by examing 100 subjects (88 males and 12 females) who were referred for diagnostic coronary angiography. The left main coronary artery, right coronary artery, the circumflex artery, and the left anterior descending artery were assessed and graded for degree of occlusion on a 5 point scale. A semi quantitative estimate of atherosclerotic mass was obtained by multiplying the scores of long (≥5 mm) lesions by 2 and giving an additional score of 1 to each segment with stenotic lesions in its peripheral branches. Coronary atheromatosis scores were the sum of each of the components. These scores were then divided into tertiles, with the highest tertile compared to the other two. The dental index score was a combined score for dental caries and periodontal infections. No associations between dental infections and coro nary atheromatosis were found for the 12 females. In a multivariate analysis, significant associations were found between dental infections, age, and triglycerides and

severe coronary atheromatosis. These associations remained significant even though total cholesterol, HDL cholesterol, smoking, hypertension, socioeconomic status, and body mass index (BMI) were in the model and non-significant. The authors discussed the fact that bacterial infections and compounds have profound effects on endothelial cells, monocyte-macrophages, thrombocytes and blood coagulation, and lipid metabolism and concluded that dental infections are the only factor outside the scope of the classic coronary risk factors which have shown an independent association with the severity of adult coronary atherosclerosis in multivariate assessment.

DeStefano and colleagues (1993) investigated coronary heart disease and mortality by following the subjects for 14 years. This study examined several potentially confounding variables including age, sex, race, education, marital state, systolic blood pressure, total cholesterol levels, BMI, diabetes, physical activity, alcohol consumption, poverty, and cigarette smoking. They demonstrated that among the nearly 10,000 subjects analyzed, those with periodontitis had a 25% increased risk of coronary heart disease relative to those with minimal periodontal disease, adjusted for the covariables mentioned above. In men younger than 50 years of age, periodontal disease had an effect on coronary heart disease incidence, with a relative risk of 1.72. This study provides evidence for an association between periodontal disease and CHD and supports the finding of earlier, smaller studies by Mattila et al., (1989) that showed an association between periodontal disease and acute myocardial infarction and atherosclerosis.

Mattila et al., (1995), followed 182 males and 32 females who had experienced myocardial infarction to determine the patients coronary outcomes, which were new fatal and non-fatal coronary events, and overall mortality. The baseline dental measures were the total dental index (which included caries, periodontitis, periapical lesions, and pericoronitis) and pantomography index (number of vertical bone pockets, furcations, and periapical lesions, and lesions caused by fourth degree caries or pericoronitis) recorded at the time of first admission for a myocardial infarction. Cox proportion hazards models were developed for the 52 patients who met the outcome criteria. The total dental index was significant in a model that included the pantomography index, number of previous infarctions, diabetes, BMI, hypertension, smoking, total cholesterol, HDL cholesterol, triglycerides, socioeconomic status, gender, and age. Conversion of the Cox coefficients to hazard ratio for the total dental index was 1.2. Thus, for each unit increase in the total dental index, the hazard ratio for new coronary events increased by a factor of 1.2.

Beck et al., (1996), conducted analyses on men who were systemically healthy at the time of the dental examinations. Mean bone loss scores and worst probing depth scores per tooth were measured on 1.147 men during 1968–1971 and again during a follow-up examination 18 years later. Over the 18 years, 207 men developed coronary heart disease, 59 died of CHD, and 40 had strokes. Incidence odds ratios adjusted for age and established cardiovascular risk factors were 1.5. 1.9 and 2.8 for bone loss and total CHD, fatal CHD, and stroke respectively. Additional results from this study investigating the relationship between probing depth at baseline and subsequent CHD, fatal CHD, and stroke indicated that the extent of sites with probing depths > 3 mm was strongly related to the incidence of total CHD, with an age-adjusted incidence odds ratio of 3.6 and an odds ratio of 3.1 when adjusted for other relevant risk factors. The patterns for probing depth and fatal CHD and stroke were similar but non-significant, probably due to the small sample size associated with these conditions.

Joshipura et al., (1996), followed 44,119 men in the health professions who had no reported CHD symptoms at baseline. The authors reported no association between periodontal disease and CHD, with a relative risk of 1.04 (95% CI = 0.86, 1.25) when controlling for age, body mass, exercise, smoking habits, alcohol consumption, family history of myocardial infarction before age 60, and vitamin E. However men who had 0–10 teeth compared to men with 25 or more teeth had a relative risk of 1.40.

Genco et al., (1997), investigated the association between periodontal infection and risk of cardiovascular disease in 1.372 Native Americans of Indian Community a group with a high prevalence of diabetes mellitus. At baseline, alveolar bone level was assessed and cardiovascular status was monitored for up to 10 years by using electrocardiograms. New cardiovascular disease occurred in 68 people. Among all age groups, bone level was predictive of cardiovascular disease (CVD) but did not remain significant in a multivariate analysis. However, for person ≤ 60 years of age, bone level was predictive of CVD, with an odds ratio of 2.68 (95% CI = 1.30, 5.5), adjusting for the effects of gender and duration (10 years) of diabetes.

Briggs et al., (2006), investigated possible association between coronary heart disease (CHD) and chronic periodontitis in a population of middle-aged males. 92 males aged over 40 years with angiography proven CHD and 79 aged matched males, with no evidence of CHD, as a control were randomly selected from the

same locality. High sensitivity c-reactive protein (CRP) was measured in serum by immunoturbidimetry. Subjects with ≥ 4 mm pocketing in more than 20% of their interproximal sites and those with deep pocketing (≥ 6 mm) were classified as having poor periodontal status. A total of 35 cases in test group (38%), compared to only 13 cases in control (16%), had a poor periodontal status. Men with a poor periodontal condition had a higher levels of CRP (median 2.19 mg/l) than those with good periodontal health (median 1.42 mg/l). After adjusting for smoking, academic achievement, alcohol consumption, unemployment, ability to maintain body weight, regular exercise, ability to relax daily, plaque, and CRP, logistic regression analysis showed that poor periodontal status was significantly associated with CHD, with an adjusted odds ratio of 3.06 and 95% confidence intervals of 1.02–9.17. It was concluded that there was an association between coronary heart disease and poor periodontal status in the middle aged males investigated. This association was independent of diabetes and all other cardiovascular risk factors investigated.

Ylostalo et al., (2006), investigated relationship between dental disease and diagnosed angina pectoris, in 6033 subjects. Gingivitis, dental caries and tooth loss were determined on the basis of self-reported gingival bleeding, presence of dental caries and six or more missing teeth. It was found that overall association of gingivitis confidence interval, dental caries and tooth loss with the presence of angina pectoris. The association were modified by gender and socioeconomic status. In addition, gingivitis, dental caries and tooth loss were also associated with several cardiovascular risk factors. It was reported that there were positive association between self-reported gingivitis, dental caries and tooth loss with angina pectoris.

Gotsman et al., (2007), evaluated the relationship between extent and severity of periodontal disease and severity of Coronary artery disease (CAD) as well as acute clinical cardiac status of the patients undergoing diagnostic coronary angiography. Two hundred and one patients presenting with stable angina or acute coronary syndromes (ACSs) referred for coronary angiography underwent a periodontal assessment which included plaque index (PI), gingival index (GI), bleeding on probing (BOP) and probing depth (PD). In addition, specific subgingival periodontal pathogens were assessed in pooled bacterial samples from the three deepest periodontal pockets of each patient. They observed that the patients with severe Coronary artery disease defined by multiple vessel disease

had significantly more periodontal destruction than those with mild coronary artery disease as shown by mean clinical attachment level, a measure of chronic periodontal disease. Logistic regression analysis showed that percentage of teeth with clinical attachment level ≥ 5 mm was significantly associated with coronary artery disease severity.

Studies reviewed indicated that the association between oral-conditions and CHD are remarkably consistent across different population samples and different measures of periodontitis (bone loss probing depth). In addition, the longitudinal studies using incident CHD events as an outcome indicated that the oral conditions preceded the heart conditions, with the other longitudinal study relating oral conditions to new coronary events following a first myocardial infarction. The available evidence does allow an interpretation of periodontitis being a risk factor for atherosclerosis/CHD, although it is a close call. While level of association would result in oral conditions contributing to a large number of CHD cases, it is possible that associations of small magnitude are due to various types of bias that may have occurred in the studies. Furthermore, all of the longitudinal studies presented were secondary analyses from data not specifically gathered to investigate this association. Thus, confirmation of these association from studies designed for this purpose would be comforting. Especially useful would be confirmation from intervention studies.

Reviewing the evidence on specificity of associations indicates that these oral conditions atherosclerosis/CHD associations remain significant, even when controlling for relevant, established risk factors. Although some exposures such as smoking indeed have been shown to be risk factors for multiple conditions, such as heart disease, cancer, and periodontal disease. Therefore, there is always the possibility that some confounder not previously measured could account for the associations seen. Therefore more convincing data are needed to support the current findings related to this association.

Influence of Periodontal Pathogens

Cardiovascular diseases, including atherosclerosis and myocardial ischemia (MI), occur as a result of a complex set of genetic and environmental factors. The genetic factors include age, lipid metabolism, obesity, hypertension, diabetes, fibrinogen levels, and platelet PI A2 polymorphism. Environmental risk factors include socioeconomic status, exercise, stress, diet, dosing with non-steroidal anti-inflammatory drugs (NSAIDs), smoking, and chronic infections. Indeed,

microbial pathogens associated with chronic infections may contribute to the risk of cardiovascular diseases. For example, the pulmonary pathogen *Chlamydia Pneumoniae* is believed to disseminate through the blood to infect the vascular endothelium and contribute to the occurrence of atherosclerosis. As shown by immunofluorescent techniques, antigens *of* C. *Pneumoniae* localize to atherosclerotic plaques with a high prevalence in individuals with prior coronary bypass surgery. Notably, control specimens of coronary arteries obtained from individuals without clinical signs of coronary artery disease rarely show evidence of C. pneumoniae infection. Other microbes implicated in the pathology of atherosclerosis include Helicobacter pylori, and Herpes simplex virus type 2(Vercelotti GM;1995).

Dental infection may also contribute to the risk of atherosclerosis and MI (Mattila et al., 1993). A recent preliminary report indicates that atherosclerotic plaques arc commonly infected with Gram-negative periodontal pathogens, including *Actinobacillus Actinomycetemcomitans* and *Porpllyromonas Gingivali (*Zambon et al.,). While the prevalenc of bacteremia secondary to pulmonary infection with C. *Pneumoniae* is not known, dental surgical procedures cause detectable bacteremias in more than 80% of patients (Durack et al., 1995). Simple oral hygiene procedures applied at home cause bacteremia in at least 40% of individuals. It is likely, therefore, that exposure to dental microorganisms over a lifetime occurs far more frequently than to any other atherosclerosis associated microbes.

As atherosclerotic lesions develop in the coronary arteries, the risk gradually increases for occurrence of myocardial ischemia and infarction. Most cases of myocardial infarction are precipitated by the occurrence of thrombosis, resulting in coronary arterial occlusion. Thus, some risk factors for myocardial infarction may act chronically to contribute to atherosclerosis; others may promote thrombosis and more directly contribute to acute coronary artery occlusion. Thrombosis may result in coronary artery occlusion even in the absence of chronic risk factors. In the presence of chronic risk factors, microthrombosis is prominent during the development of atherosclerotic plaques and is followed by fibrous scarring and the accumulation of macrophages, cholesterol crystals, and thickening of the myointima. The narrowed, injured atherosclerotic lumen and the presence of vasospasm might increase the chance of occlusion of the coronary arteries by subsequent acute thromboembolic events.

Established risk factors for myocardial infarction which may be chronic contributors include NSAID dosing, exercise, diet, stress, lipid metabolism,

smoking, and infections with lipopolysaccharide (LPS)-containing bacteria. In each case, these risk factors appear to affect the pathogenesis of atherosclerosis. In contrast risk factors that may contribute to acute thromboembolic events include fibrinogen levels platelet PI polymorphism, stress, NSAID dosing, and infections with microorganisms, which induce platelet aggregation (Agg+ phenotype). These factors may promote coronary artery occlusion, heart ischemia, and eventually myocardial infarction. Some risk factors such as NSAID dosing, and perhaps smoking, may effect chronic risk of atherosclerosis and acute risk of thrombosis. If oral infections are risk factors for the occurrence of myocardial infarction, the bacteria may contribute to acute thrombotic events and through the chronic inflammatory pathway to atherosclerosis.

Periodontal infection may have an impact in the cardiovascular system by direct and indirect effects of oral bacteria. Periodontal bacteria, lipopolysaccharide (LPS), and other soluble bacterial components may shed from chronically inflamed periodontal lesions and enter the circulatory system, directly affecting the vessel walls. Recently, periodontal pathogens have been found in atheromatous plaques obtained in carotid (Haraszthy et al., 2000) and aortic tissues (Stelzel et al., 2002). Periodontal infection may also serve as an inflammatory stimulus contributing to cardiovascular disease. Periodontal pathogens may increase the release and circulation of cytokines and proinflammatory mediators that may initiate a cascade of biologic events leading to endothelial damage and cholesterol plaque formation.

Nonnenmacher et al., (2007), assessed the relationship between periodontal disease and coronary artery disease (CAD) based on clinical and periodontal microbiologic parameters. A total of 90 male subjects, out of which fourty-five men had CAD (CAD+), which was confirmed by coronary angiography and forty-five age-matched controls showed no history or symptoms of CAD (CAD-). All subjects underwent a clinical periodontal examination including assessment of tooth loss, probing depth, clinical attachment level, and bleeding on probing. In the CAD+ group, the clinical examination was conducted 1 day before coronary angiography. Subgingival microbial samples were taken and evaluated by means of real time polymerase chain reaction (RT-PCR) for the total amount of bacteria for the following periodontopathogens: Actinobacillus actinomycetemcomitans, Porphyromonas gingivalis, Prevotella intermedia, Parvimonas micra, Dialister pneumosintes, and Campylobacter rectus. Compared to control subjects, CAD+ subjects had significantly deeper pockets (2.28 mm versus 2.96 mm) and

greater attachment loss (2.85 mm versus 3.65 mm), and this difference remained statistically significant after adjusting for smoking. No significant differences were observed between CAD+ and controls with regard to the number of teeth present. P.intermedia was the only periodontal pathogen that showed significantly higher mean counts of total bacteria, although P.micra, D.pneumosintes, and C.rectus were found in the CAD- group. It was concluded that a relationship between periodontal disease and coronary heart exists, although P.intermedia was the only periodontopathogen related to coronary artery disease (CAD).

Noack et al., (2001), examined the relationship between C-Reactive Protein (CRP) plasma levels and severity of periodontal disease as well as periodontal microflora to predict a risk for arthrosclerosis and CVD. 174 subjects were assessed for C-Reactive Protein using radial immunodiffusion assay, 59 with moderate mean clinical attachment loss (2.39 mm) 50 with high level mean clinical attachment loss (3.79 mm) and 65 with periodontally healthy controls (1.74mm). Clinical attachment loss, probing depth, and percentage of periodontal pockets sites $\geq$ 5 mm were measured. The presence of periodontal pathogens porphyromonas gingivalis (P.G.), Prevotella Intermedia (P.I.), Campylobacter Recta (C.R.), and Bacteroids Forsythus (B.F.) in subgingival plaque samples were measured by immunofluorosence microscopy. Statistically significant increase in C-Reactive Protein levels were observed in subjects with periodontal disease when compared to healthy controls. Subjects with high level of mean clinical attachment loss had significantly higher mean C-Reactive protein levels (4.06 mg/l) than controls (1.07 mg/l). The presence of periodontal pathogens Porphyromonas Gingivalis (P.G.), Prevotella Intermedia (P.I.), Campylobacter Recta (C.R.), and Bacteroids Forsythus (B.F.) in subgingival samples were positively associated with CRP levels. It was concluded that the positive correlation between CRP and periodontal disease might be a possible underlying pathway in the association between periodontal disease and the observed higher risk for cardiovascular disease in these patients.

Zaremba et al., (2007), assessed the incidence of selected anaerobic bacteria in Subgingival and atherosclerotic plaque in 20 patients treated surgically for coronary vessel obliteration. Subgingival plaque was collected from periodontal pocket > 5 mm. DNA testing was used to identify eight pathogens responsible for periodontal tissue destruction. Material from atherosclerotic plaque was collected from the same patients during bypass surgery, and DNA testing by the same method was performed. In 13 of 20 patients, the pathogens most frequently found in severe

chronic periodontitis were also found in coronary vessels. In 10 cases, those species of bacteria were also present in atherosclerotic plaque. The most frequently identified bacteria were Porphyromonas gingivalis and Treponema denticola. It was concluded that in patients with severe form of chronic periodontitis, the clinical attachment loss was not associated with bacterial permeability into the coronary vessels.

Pucar et. al (2007), examined biopsy samples of coronary and internal mammary arteries for the presence of putative pathogenic bacterial (Porphyromonas gingivalis, Actinobacillus actinomycetemcomitans, Prevotella intermedia, and Tannerella forsythensis), Chaamydia pneumoniae, and human cytomegalovirus (CMV). 15 patients with a diagnosis of coronary artery disease were included in the study. Fifteen coronary arteries with atherosclerosis and 15 internal mammary arteries without clinically assessable atherosclerotic degeneration were investigated. Both groups of specimens were obtained during coronary artery bypass grafting surgery, from the same patient. The detection of periodontal pathogens, C.pneumoniae, and CMV was done by polymerase chain reaction analysis. Bacterial DNA was found in nine of 15 (60%) coronary artery biopsy samples: P. gingivalis in eight (53.33%), A. actinomycetemcomitans in four (26.67%), P.intermedia in five (33.33%), and T. forsythensis in two (13.33%) samples; CMV was detected in 10 (66.67%) samples, and C, pneumoniae was detected in five (33.33%) samples. Some of the samples contained more than one type of bacteria. Periodontal pathogens were not detected in internal mammary artery biopsies, whereas was CMV present in seven (46.67%) samples and C, pneumoniae was present in six (40%) samples. It was concluded that the absence of putative pathogenic bacteria in internal mammary arteries, which are known to be affected rarely by atherosclerotic coronary arteries support the concept that periodontal organisms are associated with the development and progression of atherosclerosis.

Haraszthy et al., (2000), examined 50 carotid endarterectomy samples using eubacteria-specific PCR; 22 were positive for various bacteria, including Tfin 30%, *Pg* in 26%, *Pi* in 14%, and *Aa* in 18%. Taylor-Robinson et al., (2002) detected *Aa* and/or *Pi* in 31% of various arterial specimens. This rate was almost as high as the rate of detection of C.*Pneumoniae* (35%). Using in vitro invasion assay, Dorn et al., (1999), found that certain strains of *Pg* and *Pi* were able to invade coronary artery cells. In the same study, transmission electron microscopy showed numerous *Pg* and *Pi* present intracellulary in coronary artery cells. *Pg* also has been detected in atherosclerotic plaques using immunocytochemical and in situ

hybridization methods (Chiu B; 1998), *Treponema Detincola* was found in six out of 26(23.1%) atherosclerotic lesions, and immunofluorescence microscopy with specific anti- T. denticola anitbodies demonstrated aggregated antigenic particles in a thin section of the PCR-positive samples (Okuda et al., 2001), Okuda et al., (2004) detected Pg, Aa, Campylobacter rectus, Tf, and T. denticola DNA in coronary arterial walls. These findings represent clear evidence that periodontal pathogens enter the circulation, causc transicnt bactcrcmia, and then can lodge in diseased blood vessel walls.

Streptococcus sanguis is the most prevalent species in dental plaque and frequently identified in the polymicrobial bacteremias from dental foci (Watanakunakorn et al., 1993). Platelet aggregating strains (Agg+) of S. sanguis induce aggregation of human platelet in vitro (Herzberg et al., 1983). This phenomenon is mediated by the expression of the platelet aggregation-associated protein (PAAP) on the surface of certain strains. Agg+ S. sanguis appears to interact with circulating platelets during bacteremias, resulting in the formation of thromboemboli. These thromboemboli can then occlude coronary arteries to cause transient myocardial ischemia. Dental bacteremias and other septic infection may also contribute to inflammatory vascular disease, Agg+ microorganisms may contribute directly to thrombosis and coronary artery occlusion. In the absence of known coronary artery disease, these report provide evidence suggesting a cause-and-effect relationship between dental bacteremias and thromboembolic events leading directly to myocardial ischemia. Indeed, our data are consistent with the conclusion that experimental Agg+ S, *sanguis* bacteremia causes thromboemboli that obstruct coronary arteries to produce transient myocardial ischemia.

During periodontal disease, Gram-negative organisms such as P. gingivalis appears with high frequency. These Gram-negative bacteria may contribute to lipopolysaccharide {LPS}-mediated damage to the endothelium by primary macrophages and other inflammatory cells (Beck et al., 1996) and generating inflammatory cytokines (Wang et al., 1996). Through these mechanisms, dental infections may contribute to the progression of atherosclerosis as suggested for chronic pathogens affecting other organs.

P. gingivalis, however, also expresses the Agg+ phenotype and a PAAP cross-reactive antigen (Herzberg et al., 1994). Other putative Gram-negative periodontal pathogens have not been observed to express the Agg+ phenotype. If the Agg+ phenotype should be shown to be generally thrombogenic, one could speculate that

P. gingivalis, as a predominant putative periodontal pathogen, may contribute to both the chronic LPS-mediated and Agg+- mediated pathways to atherosclerosis and thrombosis.

The distribution of putative periodontal pathogens in 60% of the atheromatous coronary arteries and their absence in clinically healthy IMAs contrasted with equal numbers of infections of C.Pneumoniae and human CMV in both vessel types. This suggested that periodontal organisms are more likely than the other two organisms to be of etiological significance in atherosclerosis.

Experimental animal studies (Li et al., 2002) suggested that intravenous administration of Pg enhanced atheroma formation and calcification in apolipoprotein E-deficient (ApoE)-null mice. Pg induced lipid accumulation in accordance with the severity of periodontitis in New-Zealand white rabbits (Jail et al., 2003). Recurrent Pg bacteremia induced aortic and coronary lesions consistent with atherosclerosis normocholesterolemic pigs and increased aortic and coronary atherosclerosis in hytercholesterolemic pigs (Brodala et al., 2005). Despite convincing results, data from animal models studies should be taken with caution, because the exposure of animals to periodontal pathogens in these models much greater than that encountered during naturally occurring periodontitis (Armitage, 2000).

Influence of Periodontal Inflammatory Stimulants

Infection has been recognized as a risk factor for atherogenesis and thromboembolic events. In fact this possibility has been recognized for decades. Gram-negative bacteria or the associated lipopolysaccharide (LPS,endotoxin),when presented as a systemic challenge in animal models, can induce inflammatory cell infiltration into major blood vessels, vascular smooth muscle proliferation, vascular fatty degeneration,and intravascular coagulation. The remarkable similarities of bacterial-induced vascular pathology and the natural history of atherogenesis have led certain invest igators to suggest that in addition to genetic and dietary inf1uences, infections of unknown origin may contribute to the observed cardiovascular pathology. Periodontitis has been proposed as having an aetiological or modulating role in cardiovascular and cerebrovascular disease. Several mechanisms have been proposed to explain or support such theories. One of these is based around the potential for the inflammatory phenomenon of periodontitis to have effects by the systemic dissemination of locally produced mediators such as C-reactive protein (CRP), interleukins -1 beta (IL-1β) and -6 (IL-6) and tumour necrosis factor alpha (TNF-α) (Gemmel et al., 1997, Kornman et al., 1997). A series of investigations

have suggested that the levels of these molecules can predict increased risk of cardiovascular disease (Lindberg et al., 1991, Liuzzo et al., 1994). Furthermore, it has been proposed that patients with periodontitis may have elevated circulating levels of some of these inflammatory markers.

The acute-phase response is a non-specific process that may occur in the initial host response to infections. It is initiated by the activation of local macrophages and other cells including fibroblast and endothelial cells, leading to the release of mediators such as TNF-α, IL-6 and lL-Iβ. These in turn cause systemic changes including hepatic release of a range of plasma proteins including CRP, activation of complement proteins and various metabolic changes (Capelli et al., 2000). Il-6 also promotes induction of fibrinogen (fib), hapatogloblin, α1-antitrypsin and α2-macrogloblin among others. CRP and other acute phase molecules are usually present at relatively low levels in plasma, but mmay be raised dramatically within 72h of tissue injury or with infection. CRP opsonises bacteria for complement binding and activates complement when complexed. CRP, IL1β and TNF-α have been associated with the presence of various bacterial infections including periodontitis (Borden et al., 1994).

Over the past decade, an individual's CRP level, as a marker of the systemic inflammatory response and measured years before known CVD, has been associated consistently with incident CHD in the general population (Kuulasmaa et al., 2000). This elevation in CRP may reflect the burden of subclinical atherosclerosis in a person because the atherosclerotic process is inflammatory in nature. CRP is found within atheromas and is generated by the atheromatous process. Endothelial cells in atheromatous lesions locally produce CRP, as measured by in situ mRNA, and macrophage-derived IL-6 originating in the atheroma can elicit further hepatic generation of CRP. As such, CRP has been seen simply as a marker for an individual's total atheromatous burden.

CRP also has been documented to play a direct role in the progression of atheromatous disease (Bhakdi et al.,1999). In support of this, CRP was shown to opsonize oxidized (LDL) cholesterol, allowing for complement activation as well as macrophage uptake, leading to the characteristic foam cell generation associated with atheroma formation (Bhakdi et al., 2001). In these studies, neither native nor modified LDL cholesterol induced foam cell generation, as a measure of atherogenic potential, in the absence of CRP. Thus, the epidemiologic association between CRP and CVD also may reflect an increased risk conferred by CRP itself. As such, it has been proposed that CRP arising from the liver in response to distant

sites of chronic infection, including periodontal disease, may become deposited in atheromas and contribute to their accelerated progression.

Independent of a systemic response with CRP, however, the direct deposit of periodontal-derived bacteria within atheromas also has been proposed as an inflammatory stimulus leading to atheromatous progression. Periodontal pathogens have been detected within atheromatous plaques (Pucar et al., 2007 & Hereszthy et al., 2000) where they may activate endothelial cells and monocytes when taken up by bacterial pattern recognition Toll-like receptors. It was proposed that by activating macrophages, these macrophages are also stimulated to recognize modified LDL cholesterol by molecular mimicry (thus the Toll-like receptors also are known as cholesterol-scavenger receptors), leading to foam cell generation and atheroma progression.

Montebugnoli et al., (2004), assessed the relationship between poor oral health and coronary heart disease (CHD) and systemic inflammatory and haemostatic factors. The study population consisted of 63 males aged 40–65 years with proven coronary heart disease (CHD), and 50 controls matched for geographic area and socioeconomic status. Oral status was recorded using four different dental indices. Blood samples were taken for measurement of the following CHD risk factors: serum total cholestral, triglycerides, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholestral, and glucose; a series of systemic markers of inflammation (C-reactive protein, leucocytes, fibrinogen, homocysteine) and a series of haemostatic factors (von Willebrand factor, fibrin, fibrin D-dimer, prothrombinic fragment F1,2, plasminogen activator inhibitor type I (PAL-I), and serum antibodies) against oxidized LDL (anti-Ox-LDL). Multiple logistic regression adjusted for all risk factors for CHD showed statistically significant relationship between all dental indices and CHD. Significant relationship were also found between TDI and the von Willebrand factor, and between CPSS and the von Willebrand factor, anti-Ox-LDL, and PAI-1. They observed positive association between poor oral status and CHD, and provides evidence that inflammatory and haemostatic factors could play an important role in this association.

Tuter et al., (2007), determined GCF and serum levels of high-sensitivity C-reactive protein (HsCRP) in chronic periodontitis (CP) patients with or without coronary artery disease (CAD). Thirty chronic periodontitis patients with angiographically proven coronary artery disease (CAD), 20 chronic periodontitis patients, and 17 healthy individuals were included. Clinical parameters were recorded, and serum and GCF samples were collected. The levels of HsCRP in

GCF was assayed by a high-sensitivity enzyme-linked immunosorbent assay. The HsCRP level was assayed in the plasma on a nephelometer. The serum HsCRP levels were significantly higher in chronic periodontitis patients with or without coronary artery disease than in the control group, and there was a correlation between serum HsCRP levels and clinical parameters and between serum HsCRP levels and GCF volume. There was no statistically significant difference in GCF HsCRP levels between the groups. There was no correlation between GCF HsCRP levels and clinical parameters, GCF volume, or serum HsCRP levels. Patients with CP and CP+CAD had statistically significant elevations in serum HsCRP levels compared to healthy subjects. It was concluded that, HsCRP levels of GCF did not differ from those of the control and CP groups or the control and CP+CAD groups.

Czerniuk et al., (2006), evaluated periodontal disease (PD) influence on changes in high-sensitivity C-reactive protein (hsCRP) concentration in patients with acute coronary syndromes and coexistent periodontal disease (PD). The study involved a group of 50 patients below 60 years of age consisting of nine females and 41 males. All patients had chest pain for less than 12 hour and were treated for acute coronary syndrome. The following measurements were recorded: probing depth (PD), clinical attachment loss (CAL), plaque index (PI) and bleeding index (BI) The patients were divided into two groups on the basis of own-constructed combined PD score (group 2; more advanced; and group 1; less advanced PD) as well as clinical attachment loss (CAL)-group 4: CAL > 3 mm; group 3: CAL ≤ 3 mm. Blood samples for hsCRP estimation were taken at admission, after 10/12 days and long term after acute coronary syndromes. A statistically significant decrease in hsCRP was observed among three consecutive blood samples examinations in groups 2 and 4, whereas it was only seen between examination 1 and examination 2 in groups 1 and 3. It was concluded that no statistically significant difference of hsCRP was found between studied groups, patients with less advanced PD, either estimated with the use of own-constructed combined score or on the basis of CAL, have significantly longer diminution of inflammatory response monitored with hsCRP concentration.

Persson et al., (2005), assessed the relationship between periodontal status and hsC-rp serum levels in consecutive hospitalized subjects diagnosed with acute myocardial infarction (AMI). 85 subjects with acute myocardial infarction (AMI) were carefully matched with subjects (gender, age, social, ethnic and smoking habits) without clinical evidence of cardiovascular disease (CVDs).hsC-rp levels, other routine serum values, clinical and periodontal conditions were studied.

Periodontal examination included a full mouth radiographic assessment and their routine clinical examination for the extent of bleeding on probing (BOP), probing depth (PPDs), and attachment levels. The extent of alveolar bone loss (ABL) was measured from the cement enamel junction (CEJ) to the bone level (BL) on radiograph by using a distance CEJ-BL≥4.0 mm. Subjects with acute myocardial infarction (AMI) had higher hsC-rp levels than control subjects. The odd subjects in the control group with periodontitis (≥33% or more sites with >4.0mm loss of alveolar bone) had serum hsC-rp>1.8 mg/l was 1.5 (95% CI—1.1-7.3). Linear regression analysis failed to include periodontal parameters in an explanatory model to hsC-rp values. Only the serum leukocyte (WBCs) counts were explanatory to hsC-rp values (standard coefficient = 0.45, t = 3.2). Serum WBCs count were significantly higher in control subjects with periodontitis but not in subjects in the acute myocardial infarction (AMI) group. It was concluded that 1) Elevated serum hsC-rp concentration and serum WBC counts were associated with acute coronary heart disease. 2) Elevated serum hsC-rp values were associated with radiographically defined periodontitis in subjects with no evidence of cardiovascular disease. 3) Periodontal parameters were not explanatory to elevated serum hsC-rp values if serum WBC and low density lipoprotein counts are included in the expression model.

Bruno et al., (2000) investigated whether C-reactive protein (CRP) and other systemic markers of inflammation as risk factor for cardiovascular disease were elevated in periodontitis. 107 untreated patients were included for periodontal treatment and 43 subjects in the same age range without periodontitis were taken as controls. Patients with generalized periodontitis and localized periodontitis had higher median C-reactive protein (CRP) levels than controls (1.45 and 1.30 versus 0.90 mg/l respectively), 52% generalized periodontitis patients and 36% of localized periodontitis patients were sero-positive for interleukin-6(IL-6), compared to 26% of controls. Plasma IL-6 levels were higher in periodontitis patients than in controls. Leukocytes were also elevated in generalized periodontitis (7.0 X 10^9/L, respectively). IL-6 and CRP correlated with each other, and CRP and IL-6 levels correlated with neutrophils. Periodontitis resulted in higher systemic levels of CRP, IL-6, and neutrophils. It was concluded that these elevated inflammatory factors may increase inflammatory activity in atherosclerotic lesions, potentially increasing the risk for cardiac or cerebrovascular events.

Kobayashi et al., (2007), evaluated that whether the IL-1 and FcyR gene polymorphisms represent a common risk factor for rheumatoid arthritis (RA) and periodontitis. The study population consisted of adults with RA (RA group;

N=100), periodontitis only (P group; N=100), and healthy individuals with no systemic or oral disease (H group; N=100). Clinical periodontal conditions was defined by measurements of probing depth, clinical attachment level, and bleeding on probing. Genomic DNA was isolated from peripheral blood and analyzed for determination of IL-1 genotype (IL-1A+4845, IL-1B+3954, and IL-1RN+2028) and FcyR genotypes (FcyRIIA, FcyRIIIA, and FcyRIIIB) by allele-specific polymerase chain reactions. Among 100 patients with rheumatoid arthritis (RA), 86% showed periodontal tissue destruction. However, the rheumatoid arthritis (RA) group exhibited milder levels of periodontal tissue destruction than the P group. There was a significant difference in the distribution of IL-1B+3954 C/T genotypes between the rheumatoid arthritis (RA) and periodontitis group and between the rheumatoid arthritis (RA) and healthy individuals with no systemic or oral disease (H group), with enrichment of the T allele in the rheumatoid arthritis (RA) group. The result failed to show that IL-1 and FcyR gene polymorphisms constitute a common risk factor for rheumatoid arthritis (RA) and periodontitis. It was concluded that the distributions of IL-1B+3954 genotypes and IL-1A+4845 and IL-1B+3954 haplotypes were unique to the patients with rheumatoid arthritis (RA) and periodontitis.

Btytkoglu et al., (2006), compared gingival crevicular fluid (GCF) levels of tissue-type plasminogen activator (t-PA), its inhibitor plasminogen activator inhibitor-2 (PAI-2), interleukin-1β (IL-1β), prostaglandin E2 (PGE2) in rheumatoid arthritis (RA) patients and periodontally diseased (PD) control group. Twenty-three rheumatoid arthritis (RA), 17 systemically healthy patients with periodontal disease (PD), and 17 systemically and periodontally healthy subjects were recruited. GCF samples were obtained from two single-rooted teeth and analysed using relevant ELISA kits. Total amounts of t-PA, PAI-2 and PGE2 in GCF samples of the healthy control group were significantly lower than the other group. The rheumatoid arthritis (RA) group exhibited a higher total amount of t-PA in GCF samples than the periodontally diseased (PD) group. PAI-2, IL-1β and PGE2 total amounts were similar in rheumatoid arthritis (RA) and periodontally diseased (PD) group. The coexistence of rheumatoid arthritis (RA) and periodontitis does not seem to affect clinical periodontal findings or systemic markers of rheumatoid arthritis (RA). It was concluded that similar inflammatory mediator levels in rheumatoid arthritis (RA) and periodontally diseased (PD) groups, despite the long-term usage of corticosteroids, non-steroidal anti-inflammatory drugs, suggested that rheumatoid arthritis (RA) patients may have a propensity to overproduce these inflammatory mediators.

Bozkurt et al., (2000), compared interleukin-6 (IL-6) levels in gingival crevicular fluid (GCF) and clinical periodontal findings in patients with rheumatoid arthritis (RA) and adult periodontitis (AP). A total of 45 patients were divided into 3 groups, 15 patients with rheumatoid arthritis (RA) associated with adult periodontitis (AP), 15 patients with adult periodontitis (AP), and 15 periodontally and systemically healthy subjects. Plaque Index (PI), gingival index (GI), sulcus bleeding index (SBI), probing depth (PD), and attachment level (AL) values for each patient were recorded. Enzyme-linked immunosorbent assay for quantitive detection of IL-6 in each GCF samples was employed. No significant differences could be detected between rheumatoid arthritis (RA) and adult periodontitis (AP) groups in the mean clinical parameter data except for mean PI value. Although the mean GCF IL-6 level in the rheumatoid arthritis (RA) group was the highest, no significant difference could be found among the groups. There was only a strong negative correlation between GCF IL-6 levels and gingival index (GI) scores in the rheumatoid arthritis (RA) group. It was suggested that the patients with rheumatoid arthritis (RA), despite increased local tissue destruction potential due to autoimmunity and higher PI levels than in the adult periodontitis (AP) patients, medication including corticosteroid and non-steroidal anti-inflammatory drugs may decrease gingival inflammation, but the synthesis and degradation of IL-6 in gingival tissue of rheumatoid arthritis (RA) patients may be different.

Leivadaros et al., (2005), assessed the arterial wall thickness and other variables associated with atherosclerosis in healthy subjects with and without periodontitis. Patients with moderate (N=34) and severe periodontitis (N=15) and controls (N=14) were recruited. Intima media thickness (IMT) of the common carotid arteries (CCA), internal carotid arteries (ICA),and bifurcation of carotid arteries (BCA) were estimated bilaterally using B-mode ultrasound. An overall intima media thickness (IMT) were calculated as mean of these six measurements. C reactive proteins (CRP), fibrinogen, and von Willbrand factor (vWf) were measured in plasma as indicators of systemic inflammation and atherosclerotic disease. Intima media thickness (IMT) for common carotid arteries (CCA) was 0.64, 0.68, and 0.69 mm for control, moderate, and severe periodontitis respectively (not significant). Intima media thickness for bifurcation of carotid arteries (BCA) did not vary among groups. Intima media thickness of internal carotid arteries (ICA) was largest for severe periodontitis (0.81 mm), corresponding values for controls and moderate periodontitis were 0.58 and 0.55 mm respectively. Severe periodontitis patients had an overall intima media thickness of 0.76mm, while moderate periodontitis patients and controls had lower values (0.64–0.65 mm

respectively). It was concluded that a full study investigating the relationship between periodontitis and atherosclerosis is warranted.

Thus, the bacterial burden of gingival plaque, the innate immunity response by CRP, and the acquired immunity serologic response can be combined reasonably as measures of the bacterial systemic exposure of periodontitis. This also was suggested by one study (Lalla et al., 2003) in mice, which showed that oral inoculations with *Porphyromonas Gingivalis (PG),* the most common periodontal pathogen in adult humans, resulted in the onset of periodontitis along, with Pg DNA in aortic tissue, an increase in IL-6 (CRP was not measurea), and an increase in homologous serum IgG response.

Several investigators (Beck et al., 2005, Loos et al., 2005 & Pussinen et al., 2005) suggested that bacterial systemic exposure may be the more pertinent biologic risk factor for CVD compared to periodontal disease per se. For example, in the Atherosclerosis Risk in Communities (ARIC) Study, Beck et a1., (2005) demonstrated that IgG antibody levels against P. Gin*giualis* had a stronger association with carotid intimamedia thickening (CIMT $\geq$ 1 mm) than the clinical examination. In another ARIC study, Beck et al., 30 demonstrated that periodontitis, as determined by clinical examination, was not predictive of CHD, whereas the systemic antibody response against multiple periodontal organisms was associated with CHD in smokers and non-smokers. Several recent studies linked biologic markers of periodontal disease exposure with cardiovascular outcomes.

Periodontal disease associated with elevated markers of bacterial systemic exposure is associated with CHD with a stronger association than clinical periodontal disease. This suggests that markers of bacterial systemic exposure are the biologically pertinent exposure in periodontal disease as regards atherosclerosis and supports inflammation at a distance as playing a role in the progression of atherosclerosis. This evidence is strong among dentate men with CHD but less so for women. There is no consistent relationship to stroke, although there is, in a very limited group of studies, to early carotid atherosclerosis. A future study of CVD should include serum markers specific to periodontal pathogens to assess for recent systemic exposure to periodontitis.

Influence of Periodontal Therapy

Evidence in humans demonstrating the beneficial effects of periodontal therapy on cardiovascular disease outcomes is limited and indirect at present. Aiuto et al.,

(2004), assessed the systemic effects of treating severe widespread periodontitis in healthy individuals by examining treatment associated changes in markers of inflammation in cardiovascular atherosclerotic diseases. 94 patients with severe generalized periodontitis were enrolled with a 6 months follow-up. Serum C-reactive protein (CRP) and interleukin-6 (IL-6) levels were assessed by high sensitivity assays. Serological and clinical periodontal parameters were evaluated at baseline, 2 and 6 months after completion of non-surgical periodontal therapy. Theses were accompanied with significant reduction in serum IL-6 and CRP concentrations. In a multivariate model, serum CRP levels were significantly associated with the outcome of the periodontal treatment after correcting for potential covariates (age, body mass index, gender, smoking) and polymorphisms in the IL-6 (-174 C/G) and IL-1A (-889) genes. A median decrease in serum CRP of 0.5mg/1 was observed 6 months after completion of periodontal therapy. Subjects with above average response to periodontal therapy (< 30 residual pockets and < 30% of sites bleeding on probing) accounted for the observed improvement in the serum CRP. Control of periodontitis, achieved with non-surgical periodontal therapy, significantly decreased serum mediators and markers of acute phase response. It was concluded that severe generalized periodontitis causes systemic inflammation.

Iwamoto et al., (2003), examined the effects of antimicrobial periodontal treatment on C-reactive protein (CRP), adiponectin, and TNF-ά levels. Fifteen chronic periodontitis patients with various systemic conditions at high risk for aterosclerosis were enrolled in the study. Patients were non-surgically treated with topical application of antibiotics and mechanical debridement of calculus once a week for 1 month. Before and after therapy, C-reactive protein (CRP) and TNF-ά levels were measured. Following antimicrobial periodontal therapy, the number of bacteria in periodontal pockets were significantly decreased. Clinically, the proportion of periodontal pockets deeper than 4mm and 6mm were significantly reduced from 30.3%–28.7%, and from 24.1%–14.0%, respectively. The initial CRP value in the study population varied from 87–6,150 ng/ml. After periodontal treatment the mean C-reactive protein (CRP) value decreased significantly from 1,677.0–934.3. Initial TNF-ά concentration also varied from patient to patient. However, circulating mean TNF-ά concentration were significantly reduced following treatment, from 2.1–1.7pg/ml. In contrast to CRP and TNF-ά, serum adiponectin levels did not change significantly. It was concluded that elevated levels of CRP and TNF-ά may be associated with increased risk for future development of atherosclerosis in periodontitis patients.

Ide M.et al., (2003), evaluated the effects of periodontal treatment on circulating levels of cardiovascular and systemic inflammatory markers. 39 subjects, were divided into 2 groups, group A immediate treatment included 24 subjects and group B delayed treatment included 15 subjects. Demographic and clinical data were collected and venous blood was taken before and either 6 weeks after completion of treatment or after an equivalent 3 month control period. Periodontal examination included probing depth, loss of attachment, plaque scores and bleeding scores. Blood was analyzed to determine serum and plasma fibrinogen, C-reactive protein, sialic acid, tumour necrosis factor-ά and interleukin-6 and -1β. There were no significant differences between groups at baseline in terms of age, number of teeth, reported oral hygiene and reported previous smoking habits. There were significant improvements in the periodontal health of the treatment group compared to control subjects, with a reduction in plaque and bleeding scores, and in probing depths. However, there were no statistically significant changes in levels of any of the systemic markers. It was concluded that improvement in periodontal health may did not influence the levels of cardio vascular inflammatory markers.

Montebugnoli et al., (2005), assessed the effect of periodontal improvement after intensive dental care on patients with proved CHD along with a change in systemic inflammatory and haemostatic factors. The study population consisted of 18 males aged 40–65 years with proven coronary heart disease (CHD) and elevated values of systemic inflammatory and haemostatic factors. Blood samples were taken for measurement of the following systemic markers of inflammation [(C-reactive protein (CRP, leucocytes, fibrinogen)] and haemostatic factors [(von Willebrand factor, fibrin D-dimer and oxidized-low density lipoprotein (Ox-LDL)]. All parameters were determined in each subjects at baseline, after 4 months as a control and 3 months after an intensive protocol of scaling and root planing. No statistical difference was found between values at baseline and at the 4-month-control. All oral indices showed a significant decreased 3 months after periodontal treatment. All systemic inflammatory indices decreased but only the decrease in CRP reached statistical significance. A significant decrease was found as regards to Ox-LDL among haemostatic factors. It was concluded that an association between poor oral status and CHD, and provide evidence that the improvement of periodontal status may influence the systemic inflammatory and haemostatic situation.

Elter et al., (2006), also report decreases in these serum biomarkers plus improved endothelial function (i.e, flow-mediated dilation of the brachial artery) for 22 periodontitis patients treated with ‘complete mouth disinfection’ (i.e, scaling

and root planing, periodontal flap surgery and extraction of hopeless teeth within a 2-week period.

Seinost et al., (2005), tested endothelial function in 30 patients with severe periodontitis and compared this with 31 periodontally healthy control subjects. Before the interventions, flow-mediated dilation was significantly lower in patients with periodontitis than in control subjects.

Periodontitis patients with favorable clinical responses to non-surgical periodontal therapy (i.e., scaling and root planing, topical and peroral antimicrobials plus mechanical retreatment) exhibited concomitant improvements in flow-mediated dilation of the brachial artery and serum C-reactive protein concentrations. While the effects of periodontal therapy on cardiovascular disease events in patients have yet to be determined, the available pilot data suggest that periodontal therapies can improve surrogate cardiovascular disease outcomes like serum biomarkers and endothelial dysfunction.

The biological basis for the hypothetical association of CVD and periodontal infections is presently unclear. Infection in general appears to be a risk factor for atherogenesis. For example, the risk for CVD may increase following chlamydial or viral infection. Bacterial products such as lipopolysaccharides likely elicit recruitment of inflammatory cells into major blood vessels, proliferation of vascular smooth muscle, vascular fatty degeneration, and intravascular coagulation. These changes are the result of the action of various biologic mediators, such as prostaglandins, interleukins, and tumor necrosis factor ex (TNFα) on vascular endothelium and smooth muscle. It may well be that the inflammatory response characteristic of periodontal disease, marked by high levels of inflammatory mediators, exacerbates the process of atherogenesis. Another mechanism proposed to explain the association between periodontal disease and cardiovascular disease suggests that oral bacteria such as S. *Sanguis* and *P. Givalis* induce aggregation of platelets through the binding of a specific surface protein which share sequence homology with a platelet-activation region of collagen. Experimental evidence demonstrating that rabbits infused with a strain of *S. Sanguis* known to induce platelet aggregation showed perturbations in blood pressure, electrocardiograms, heart rate, and cardiac contractility. Affected rabbits exhibited ischemic damage to their heart muscle at necropsy. These findings suggest that platelet-aggregating bacteria, such as S. *Sanguis* or the periodontal pathogen *P. Gingivalis,* that enter the bloodstream may increase the risk for thrombogenic events including myocardial infarction and stroke. The studies reviewed above suggest that periodontal and

other oral infections may modulate CVD and stroke. Our present knowledge, however, is incomplete. Further studies are necessary to verify and quantitate the role of oral infections in the process of alherogenesis.

A central hypothesis of periodontal medicine states that periodontal infection presents a chronic inflammatory burden at the systemic level. In addition to their products, whole bacterial pathogens can enter local host tissues where pocket epithelial integrity has been lost. In addition, pathogens like P. gingivalis and A. actinomycetemcomitans have evolved virulence factors that allow for direct tissue invasion. These systemic exposures to gram-negative pathogens, LPS and other products can trigger mediator expression and inflammatory events with consequences related to other organ systems. Prostaglandin E2, for instance, causes oxidative stress, smooth muscle contraction and low density lipoprotein (LDL) oxidation. Likewise, the cytokines IL-1b, TNF-a and interleukin 6 (IL-6) can stimulate endothelial adhesion, hyperlipemia, metabolic wasting, hepatic release of acute phase reactants and connective tissue catabolism. Many of these events have been implicated in the natural histories of systemic conditions like cardiovascular disease, preterm low birth weight, diabetes and respiratory disease.

Human cross sectional and case control studies as well as animal experiments has shown periodontitis as a potential risk for reduced fetal rate, pre-term low birth weight or other pregnancy complications. Various clinical studies have demonstrated significant relation between increasing severe periodontal disease and both low birth weight as well as a decrease gestational age. Human studies in patients with periodontitis and animal studies have suggested that P.gingivalis may be an important component in the under linked association in linking periodontitis to pre-term low birth weight. It is possible that periodontal disease may facilitate the oro-utreus transfer because of the increased bacterial load in the oral cavity and altered host immune responses during disease. An association between periodontitis and diabetes mellitus is outlined in the review. It has been assumed that the association is due to the fact that people with diabetes have a compromised ability to fight infections such as periodontal diseases. Severe periodontitis has been shown to be strongly associated with an increased risk of poor glycemic control. However, till date the impact of periodontal disease on glycemic control of diabetes and mechanism through which this occur is not clear. It is possible that periodontal disease may serve as initiators or propagators of insulin resistance, there by aggravating glycemic control. Further research is needed to clear this aspect of relationship between periodontal disease and diabetics.

The studies reviewed before suggest that periodontal disease and other oral infections may modulate cardiovascular disease and stroke. Our present knowledge however is incomplete. Further studies are necessary to verify and quantitate the role of infections in process of artherogenesis. Poor oral health characterized by inadequate hygiene resulting in the formation of extensive biofilms may promote oral colonization of respiratory pathogens. Oral bacteria may modulate the adhesion of respiratory pathogens to epithelial cell linings. Furthermore, both oral and respiratory bacteria appear to induce the release of pro-inflammatory cytokines from oral and respiratory epithelial cell lines in vitro. Extra politaing this work in vivo, the release of cytokines from mucosal surfaces is response to oral bacteria interaction may change oral-micro environment, and promote the adhesion of microbes to both oral and respiratory epithelial cells, which may facilitate the onset and or progression of respiratory disease in succesiptible individuals. It is possible that factors responsible for poor oral health may be a determining factor influencing frequency of respiratory infections in high risk group. Further research defining the factor responsible for initiating the process of infection, the underlying conditions that may modulate the progression of disease and methods to improve its management are clearly needed.

It appears highly likely that the new knowledge being gained in the discipline of periodontal medicine will serve as an impetus to further correlate medicine and dentistry. Periodontist will lead to assume larger responsibility for the over all health of the patient and eventually periodontal care may become a medical necessity. Knowledge of relevant systemic conditions needs to be more extensive to enable periodontist to interact more meaningfully with their medical colleagues. This will place new educational goals on profession. Periodontist are likely to have different diagnostic criteria and therapeutic end points than physicians for example how much a drop in glycalated hemoglobin represent a reasonable therapeutic outcome following periodontal medicine therapy in a diabetic patients? Periodontist also contribute to the metabolic disregulation associated with the development of NIDDM as evidence by impaired fasting glucose. As the many authors carefully pointed out these initial observations of an association between periodontitis and systemic disease need to be confirmed as extended. In fact, it is not yet known whether relationship between periodontal infection and systemic disease is a casual or causal relationship. Other authors look at possible mechanism where by periodontitis would affect an individual. Still other authors offer new prevention and consideration for periodontal medicine patients. Much needed to be researched about this new branch of Periodontology, periodontal medicine.

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References

1. Abraham SN, Beachey EH, Simpson WA. Adherence of streptococcus aeruginosa to fibronectin –coated and uncoated epithelial cells. Infect Immun 1983;41:1261-8.
2. Appelbaum PC, Cameron EW, Hutton WS. The bacteriology of chronic destructive pneumonia. S Afr Med. J. 1978;53:541-2.
3. Arko RJ, Genco CA. Animal chambers models for study of host-parasite interactions. Methds Enzymol 1994;235:120-40.
4. Armitage. Periodontal infections and cardiovascular disease-How strong is the association? Oral Dis 2000;6:335-50.
5. Beck, Garcia R, Heiss G, Vokonas PS, Offenbacher S. Periodontal disease and cardiovascular disease. J Periodontal 1996;67:1123-37.
6. Beck, Eke P, Heiss G, Madianos P, Couper D, Lin D, Moss K, Elter J, Offenbacher S. Periodontal disease and coronary heart disease: A reappraisal of the exposure, Circ. 2005;112:19-24.
7. Benedek-Spat E, Di Felice R, Andersen E, Cimasoni G. In vitro release of elastase from human blood and gingival crevicular neutrophils. Arch Oral Biol 1991;36:507-10.
8. Bennet W A, Lagoo-Deenadayalan S, Whitworth N S, Stopple I A, Barbar W H, Hale V 1994.
9. Bentley DW. Bacterial pneumonia in the elderly: clinical features,diagnosis, etiology, and treatment. Gerontol 1984;30:297-07.
10. Bergmans DC, Bonten MJ, Gaillard CA, et al., prevention of ventilator-associated pneumonia by oral decontamination: A prospective, randomized, double blind, placebo-controlled study. Am J Respir Crit Care Med 2001;164:382-8.
11. Bhakdi S, Torzewski M, Klouche M, Hemmes M. Complement and atherogenesis:Binding of CRP to degraded, nonoxidized LDL enhances complement activation. Arterioscler Thromb Vasc Biol 1999;19:2348-54.
12. Billings F. Chronic focal infection and their etiologic relations to arthritis and nephritis. Arch Intern Med 1912:9:484-98.
13. Borden, Chin P. Interleukin-6: a cytokine with potential diagnostic and therapeutic roles. Journal of Laboratory and Clinical Medicine 123, 824-9.
14. Bozkurt FY, Berker E, Akkuş S, Bulut S Relationship between interleukin-6 levels in gingival crevicular fluid and periodontal status in patients with rheumatoid arthritis and adult periodontitis. J Periodontal 2000;71:1756-60.

15. Briggs, McKeown PP, Crawford VL, Woodside JV, Stout RW, Evans A, Linden GJ. Angiographically confirmed coronary heart disease and periodontal disease in middle-aged males. J Periodontal 2006;77:95-02.
16. Brodala N, Merricks EP, Bellinger DA, Damrongsri D, Offenbacher S, Beck J, Madianos P, Sotres D, Chang YL, Koch G, Nichols TC. Porphyromonas gingivalis bacteremia induces coronary and aortic atherosclerosis in normocholesterolemic and hypercholesterolemic pigs. Arterioscler Thromb Vasc Biol 2005;25:1446-51.
17. Brook I, Frazier EH. Aerobic and anaerobic microbiology of emphysema. A retrospective review in two military hospitals. Chest. 1993;103:1502-7.
18. Brook I, Yocum P, Foote PAJ. Changes in the core tonsillar bacteriology of recurrent tonsillitis: 1977-93. Clin Infect Dis 1995;21:171-6.
19. Brownlee M. Glycation productions and the pathogenesis of diabetic complications. Diabetes Care 1992;15:1835-43.
20. Bruno G. Elevation of systemic markers related to cardiovascular diseases in the peripheral blood of periodontitis patients. J Periodontal 2000;71:1528-34.
21. Btytkoglu B, Buduneli N, Kardeşler L, Aksu K, Oder G, Kütükçüler N. Evaluation of t-PA, PAI-2, IL-1β and PGE2 in gingival crevicular fluid of rheumatoid arthritis patients with periodontal disease. J Clin Periodontol. 2006 Sep;33(9):605-11. Epub. 2006 Jul 20.
22. Capelli M. Initiation of acute-phase response and synthesis of cytokines. Biochimica Biophysica Acta 1317, 84-94.
23. Cecil RL, Angevine DM. Clinical and experimental observations on focal infection with an analysis of 200 cases of rheumatoid arthritis. Ann Intern Med 1938:12:577-84.
24. Christgau M, Palitzsch KD, Schmalz G, Kreiner U, Frenzel S. Healing response to non-surgical periodontal therapy in patients with diabetes mellitus: clinical, microbiological, and immunologic results. J Clin Periodontal 1998;25:112-24.
25. Collins JG, Windley HW 3rd, Arnold RR, Offenbacher S. Effects of a porphyromonas gingivalis infection on inflammatory mediators response and pregnancy outcome in hamsters. Infect Immun 1994;62:4356-61.
26. Coyler S. Oral sepsis: and some of its effects. Dent Rec 1902:20:200-06.
27. Czernuik et al., C-reactive protein in patients with coexistent periodontal disease and acute coronary syndromes. J Clin Periodontal 2006; 33: 415-20.
28. D'Aiuto F, Parkar M, Andreou G, Brett PM, Ready D, Tonetti MS. Periodontitis and atherogenesis: causal association or simple coincidence? J Clin Periodontal 2004;31: 402-11.

29. D'Aiuto F, Parker M, Andreou G, Periodontitis and systemic inflammation: Control of the local infection is associated with a reduction in serum inflammatory markers. J Dent Res. 2004;83:156-60.

30. Dasanayake AP, Li Y, Wiener H, Ruby JD, Lee MJ.Salivary Actinomyces naeslundi Genospecies 2 and lactobacillus casei levels predict pregnancy outcomes. J Periodontal 2005;76:171-77.

31. Dasanayake. Poor periodontal health of the pregnant women as a risk. Ann Periodontal 1998;3(1):206-12.

32. De Stefano, Anda RF, Kahn HS, Williamson DF, Russell CM. Dental disease and risk of coronary heart disease and mortality. BMJ 1993;306:688-91.

33. Debora C, Mario T, Arthur B, Sergio S & Marcio G, Effect of non surgical periodontal therapy on glycemic control in patients with type 2 diabetes mellitus. J Periodontal 2003;74:1361-67.

34. DeRiso AJ 2nd, Ladowski JS, Dillon TA, Justice J, Peterson AC. Chlorhexidine gluconate 0.12% and rinse reduces the incedences of total nosocomial respiratory infection and nonprophylactic systemic antibiotic use in patients undergoing heart surgery. Chest 1996;109:1556-61.

35. Diamond J. The double puzzle of diabetes. Nature 2003 ; 423: 599–602.

36. Didilescu A, Skaug N, Maria C, Didilescu C. Respiratory pathogens in dental plaque of hospitalized patients with chronic lung diseases. Clin Oral Investig 2005;9:141-7. Epub 2005 May 21.

37. Dominguez H, Storgaad H, Rask-Madsen C, et.al. Metabolic and vascular effects of tumor necrosis factor-alpha blockade with etanercept in obse patients with type 2 diabetes. J Vasc Res 2005;42:517-25.

38. Donowitz GR, Mandell GL. Acute pneumonia. Mandell GL, Douglas RG, Bennet JE. Principles and practice of infectious disease. New York: Chuchul Livingstone, 1990:540-55.

39. Durack. Prevention of infective endocarditis. New Engl J Med 1995;332:38-44.

40. Elter, Hinderliter AL, Offenbacher S, Beck JD, Caughey M, Brodala N, Madianos PN. The effects of periodontal therapy on vascular endothelial function: a pilot trial. Am Heart J 2006: 151: 47.e1-47.e6.

41. Estes RJ, Meduri GU. The pathogenesis of ventilator associated pneumonia: Mechanisms of bacterial translocation and airway inoculation. Intensive Care Med 1995;21:365-83.

42. Fagon JY. Chastre J. Severe exacerbations of COPD patients: The role of pulmonary infections. Sem Respir Infect 1996:11:109-18.

43. Faria-Almeida R, Navarro A, Bascones A. Clinical and metabolic changes after conventional treatment of type 2 diabetic patients with chronic periodontitis. J Periodontal 2006;77:591-8.

44. Fernandez-Real JM, Ricart W. Insulin resistance and chronic cardiovascular inflammatory syndrome. Endocr Rev 2003;24:278-301.

45. Finegold SM, Aspiration pneumonia. Rev Infect Dis 1991;13:S737-S742.

46. Fourrier F, Cau-Pottier E, Boutigny H, Jourdain M, Chopin C. Effects of dental plaque antiseptic decontamination on bacterial colonization and nosocomial infections in critically ill patients. Intensive Care Med 2000;26;1239-47.

47. Fourrier F, Duvivier B, Boutigny H, Roussel-Delvallez M, Chopin C. Colonization of dental plaque:A sourse of nosocomial infections in intensive care unit patients. Crit Care Med 1998;26:301-08.

48. Frandsen EG, Reinholdt J, Kilian M. Enzymatic and antigenic characterization of immunoglobin A1 protease from bacteroides and capnocytophaga spp. Infect Immun 1987;55:631-638.

49. Galloway GE. Focal infection. Am J Surg 1931:14:643-645.

50. Garrouste-Orgeas M, Chevret S, Arlet G, et al., Oropharyngeal or gastric colonization and nosocomial pneumonia in adult intensive care unit patients. A prospecrive study based on genomic DNA analysis Am J Resp Crit Care Med 1997;156:1647-55.

51. Gemmell B. Cytokines and prostaglandins in immune homeostasis and tissue destruction in periodontal disease. Periodontology 2000 14, 112-43.

52. Genco et.al. Periodontal disease is a predictor of cardiovascular disease. J Dent Res 1997;76(Spec. Issue):408 (Abstr. 3158).

53. Genco RJ, Grossi SG, Ho A, Nishimura F, Murayama Y. A proposed model linking inflammation to obesity, diabetes and periodontal infection. J Periodontal 2005;76:2075-2084.

54. Genuit T, Bochicchio G. Prophylactic chlorehexidine oral rinse decreases ventilator-associated pneumonia in surgical ICU patients. Surg Infect (Larchmt) 2001;2;5-18.

55. Gibbons RJ, Etherden I. Fibronectin-degrading enzymes in saliva and their regulation to oral cleanliness. J Periodont Res 1986;21:386-95.

56. Gibbons RJ, Hay DI, Childs WC, Davis G. Role of cryptic receptors in bacterial adhesion to oral surfaces. Arch Oral Biol 1990;35(Suppl);107S-114S.

57. Gibbs RS, Romero R, Hillier SL, Eschenbach DA, Sweet RL.A review of premature birth and sub-clinical infections. Am J Obstet 1992; 166:1515-28.

58. Godley RJ. On some of the medical and surgical complications of pyorrhea alveolaris. Dent Rec 190020:337-47.

59. Goldstein EJ, Kirby BD. Isolation of Eikenella corrodens from pulmonary infections. Am Rev Repir Dis 1979;119:55-8.

60. Golub LM, Ramamurthy NS, McNamara TF, Greenwald RA, Rifkin BR. Tetracyclines inhibit connective tissue breakdown by multiple nonantimicrobial mechanisms. Adv Dent Res 1998;12:12-26.

61. Gonzalez-Gay MA, DeMatis JM, Gonzalez C et al., Anti-tumor necrosis-alpha blockade in proves insulin resistance in patients with rheumatic arthritis. Clin Exp Rheumatol 2006;24:83-6.

62. Gotsman, Lotan C, Soskolne WA, Rassovsky S, Pugatsch T, Lapidus L, Novikov Y, Masrawa S, Stabholz A. Periodontal destruction is associated with coronary artery disease and periodontal infection with acute coronary syndrome. J Periodontal 2007;78:849-58.

63. Gracia R, Martha E, Pantel S. Epidemiologic association between periodontal disease and chronic obstructive pulmonary disease. Ann Periodontal 2001;6;71-7.

64. Gracia RI, Nunn ME, Vokonas PS. Epidemiologic associations between periodontal disease and chronic obstructive pulmonary disease. Ann Periodontal 2001;6:71-7.

65. Greets SO, Nys M, De Mol P, Systemic released endotoxins induced by gentle mastication: Association with periodontitis severity. J Periodontal 2002;73:73-8.

66. Grollier G, Dore P, Robert R, Ingrand P, Grejon C. Antibody responses to Prevotella spp. In patients with ventilator-associated pneumonia. Clin Diag Lab Immunol 1996;3;61-5.

67. Grossi RJ. Treatment of periodontal disease in diabetic reduces glycated hemoglobin. J Periodontal 1997;68:713-9.

68. Grossi SG, Genco RJ.Periodontal disease and diabetes mellitus: A two-way relationship. Ann Periodontal 1998;3:51-6.

69. Grossi SG, Skrepcinski FB, DeCaro T, Zambon JJ, Cummins D, Genco RJ.Response to periodontal therapy in diabetics and smokers. J Periodontal 41,713-8.

70. Gustke CJ. Treatment of periodontitis in the diabetic patient.A critical review. J Clin Periodontal 1999;26:133-7.

71. Hakansson A, Carlstedt I, Davies J, Mossberg A-K.Aspects on the interaction of streptococcus pneumonia and haemophilius influenza with human respiratory tract mucosa. AM J Resp Crit Care Med 1996;154:S187-S191.

72. Han YW, Ikegami A, Bissada NF, Herbst M, Redline RW, Ashmead GG. Transmission of an uncultivated Bergeyella strain from the oral cavity to amniotic fluid in a case of preterm birth. J Clin Microbiol. 2006 Apr;44(4):1475-83.

73. Haraszthy VI. Identification of periodontal pathogens in atheromatous plaques. J Periodontal 2000;71:1554-60.

74. Haraszthy VI, Zambon JJ, Trevisan M, Zeid M, Genco RJ. Identification of periodontal pathogens in atheromatous plaques. J Periodontol 2000;71:1554-60.

75. Hayes C, Sparrow D, Cohen M, Vokonas PS, Garcia RI. The association between alveolar bone loss and pulmonary function: The VA Denttal Longitudinal study. Ann Periodontal 1998;3:257-61.

76. Helovuo H, Hakkarainen K, Paunio K. Changes in the prevalence of subgingival entric rods, staphylococci and yeasts after treatment with penicillin and erythromycin. Oral Microbiol Immunol 1993;8:75-9.

77. Herzberg et.al. Phenotypic characterization of streptococcus sanguis virulence factors associated with bacterial endocarditis. Infect Immun 1990;58:515-22.

78. Herzberg et.al. The platelet as an inflammatory cell in periodontal diseases:Interactions with Porphyromonas gingivalis. Amercian Society for Microbiology;1994:247-55.

79. Holzhausen M, Garcia DF, Pepato MT, Marcantonio E Jr. The influence of short-term diabetes mellitus and insulin therapy on alveolar bone loss in rats. J Periodontal Res 2004;39:188-93.

80. Hughes RA. Focal infections revised. Br J Rheumatol 1994:33:370-7.

81. Hunter W. Oral sepsis as a cause of disease. Br Med J 1900:1:215-6.

82. Ide M, McPartlin D, Coward PY, Crook M, Lumb P, Wilson RF. Effect of treatment of chronic periodontitis on levels of serum markers of acute-phase inflammatory and vascular responses. J Clin Periodontal 2003; 30: 334-40.

83. Ingram RH. Chronic bronchitis, emphysema and airways obstruction. In: Isselbacher KJ, Martin JB, Kasper DL, etc Harrison's Principles of internal medicine. Mc Grav-New York, 1994:1197-1206.

84. Iwamoto Y, Nishimura F, Nakagawa M, et al., The effects of antimicrobial periodontal treatment on circulating tumor necrosis factor-alpha and glycated hemoglobin level in patients with type 2 diabetes. J Periodontal 2001;72:774-8.

85. Iwamoto Y, Nishimura F, Soga Y, Takeuchi K, Kurihara M, Takashiba S, Murayama Y. Antimicrobial periodontal treatment decreases serum c-reactive protein, tumor necrosis factor-alpha, but not adiponectin levels in patients with chronic periodontitis. J Periodontal 2003;74:1231-6.

86. Johanson WG, Higuchi JH, Woods DE. Bacterial adherence to epithelial cells in bacillary colonization of the respiratory tract. Am Rev Resp Dis 1969;121:55-63.

87. Joshipura, Rimm EB, Douglass CW, Trichopoulos D, Ascherio A, Willett WC. Poor oral health and coronary heart disease. J Dent Res 1996;75:1631-6.

88. Khair OA, Davies RJ, Devalia JL. Bacterial-induced release of inflammatory mediators by bronchial epithelial cells. Eur Respir J 1996;9:1913-22.

89. Kiran et al., The effect of improved periodontal health on metabolic control in type 2 diabetes mellitus. J Clin Periodontal 2005;32:266-72.

90. Kiran M, Arpak N, Unsal E, Erdoğan MF. The effect of improved periodontal health on metabolic control in type 2 diabetes mellitus. J Clin Periodontal 2005;32:266-72.

91. Kjeldsen M, Holmstrup P, Lindemann RA, Bendtzen K. Bacterial-stimulated cytokine production of peripheral mononuclear cells from patients of various periodontitis categories. J Periodontol 1995;66:139-44.

92. Knight HE. The teeth in relation to medicine. Br Dent J 1904:25:664-943.

93. Kobayashi T, Ito S, Kuroda T, Yamamoto K, Sugita N, Narita I, Sumida T, Gejyo F, Yoshie H. The interleukin-1 and Fcy receptor gene polymorphisms in Japanese patients with rheumatoid arthritis and periodontitis. J Periodontal 2007;78:2311-8.

94. Kornman et.al. Host responses in patients with generalized refractory periodontitis. Journal of Periodontology 65, 139-46.

95. Lalla E, Lamster IB, Hofmann MA, Bucciarelli L, Jerud AP, Tucker S, Lu Y, Papapanou PN, Schmidt AM. Oral infection with a periodontal pathogen accelerates early atherosclerosis in apolipoprotein E-null mice. Arterioscler Thromb Vasc Biol 2003;23:1405-11.

96. Langmore SE, Terpenning MS, Schork A, et al., Predictors of aspiration pneumonia: How important is dysphagia? Dysphagia 1998;13:69-81.

97. Leivadaros, van der Velden U, Bizzarro S, ten Heggeler JM, Gerdes VE, Hoek FJ, Nagy TO, Scholma J, Bakker SJ, Gans RO, ten Cate H, Loos BG. A pilot study into measurements of markers of atherosclerosis in periodontitis. J Periodontal 2005;76:121-8.

98. León R, Silva N, Ovalle A, Chaparro A, Ahumada A, Gajardo M, Martinez M, Gamonal J. Detection of porphyromonas gingivalis in the amniotic fluid in pregnant women with a diagnosis of threatened premature labor. J Periodontal 2007;78:1249-55.

99. Lepor M.News and reviews from the literature. Rev Cardiovasc Med 2004;5:182-5.

100. Li H. Porphyromonas gingivalis infection accelerates the progression of atherosclerosis in a heterozygous apolipoprotein E-deficient murine model. Circulation 2002;105:861-67.

101. Limeback H. Implications of oral infections on systemic diseases in the institutionalized elderly with a special focus on pneumonia. Ann Periodontal 1998;3:262-73.

102. Lin D, Moss K, Beck JD, Hefti A, Offenbacher S.Persistently high levels of periodontal pathogens associated wiyh preterm pregnancy outcome. J Periodontal 2007;78:833-41.

103. Lin D, Smith MA, Champagne C, Elter J, Beck J, Offenbacher S. Porphyromonas gingivalis infection during pregnancy increases maternal tumor necrosis factor alpha, suppresses maternal interleukin-10, and enhances fetal growth restriction and resorption in mice. Infect Immun;2003:5156-62.

104. Lindberg G, Eklund GA, Gullberg B, Råstam L. Serum sialic acid concentration and cardiovascular mortality. British Medical Journal 302, 143-6.

105. Liuzzo G, Biasucci LM, Gallimore JR, Grillo RL, Rebuzzi AG, Pepys MB, Maseri A.. The prognostic value of C-reactive protein and serum amyloid. A protein in severe unstable angina. New England Journal of Medicine 334, 417-24.

106. Loos BG. Systemic markers of inflammation in periodontitis. J Periodontal 2005;76(11 Suppl.):2106-15.

107. López NJ, Smith PC, Gutierrez J.. Periodontal therapy may reduce the risk of preterm low birth weight in women with periodontal disease: A randomized controlled trial. J Periodontal 2002;73:911-24.

108. Madianos PN, Lieff S, Murtha AP, Boggess KA, Auten RL Jr, Beck JD, Offenbacher S. Maternal periodontitis and prematurity. Part II: Maternal infection and fetal exposure. Ann Periodontal 2001;6;175-82.

109. Mahomed AG, Feldman C, Smith C, Promnitz DA, Does primary streptococcus viridians pneumonia exist? S Afr Med J 1992;82:432-4.

110. Mattila KJ, Nieminen MS, Valtonen VV, Rasi VP, Kesäniemi YA, Syrjälä SL, Jungell PS, Isoluoma M, Hietaniemi K, Jokinen MJ. Association between dental health and acute myocardial infarction. Br Med J 1989;298:779-82.

111. Mattila KJ, Valtonen VV, Nieminen M, Huttunen JK. Dental infection and the risk of new coronary events: Prospective study of patients with documented coronary artery disease. Clin Infect Dis 1995;20:588-92.

112. Mattila KJ. Dental infections as a risk factor for acute myocardial infarction. Eur Heart J 1993;14:51-3.

113. Mattila, Valle MS, Nieminen MS, Valtonen VV, Hietaniemi KL. Atherosclerosis. Dental infections and coronary atherosclerosis. Atherosclerosis Eur Heart J.1993;103:205-11.

114. Mealey BL, Ocampo GL. Diabetes mellitus. Periodontal 2000 2006;in press.

115. Miller LS, Manwell MA, Newbold D, Reding ME, Rasheed A, Blodgett J, Kornman KS. The relationship between reduction in periodontal inflammation and diabetes control:a report of 9 cases. J Periodontal 1992;63:843-8.

116. Miller WD. The human mouth as a focus of infection. Dent Cosmos 1891:33:689-713.

117. Mojan P, Budtz-Jorgensen E, Micheal J-P, Limeback H. Oral health and history of respiratory tract infection in frail institutionalized elders. Gerodontal 1988;7:131-7.

118. Montebugnoli, Servidio D, Miaton RA, Prati C, Tricoci P, Melloni C. Poor oral health is associated with coronary heart disease and elevated systemic inflammatory and haemostatic factors. J Clin Periodontal 2004;31:25-9.

119. Montebugnoli. Periodontal health improves systemic inflammatory and haemostatic status in subjects with coronary heart disease. J Clin Periodontal 2005; 32: 188-92.

120. Moore WEC, Moore LVH. The bacteria of periodontal disease. Periodontal 2000 1994;5:66-77.

121. Murphy TF, Sethi S. Bacterial infection in chronic obstructive pulmonary disease. Am Rev Respir Dis 1992:146:1067-82.

122. Nakamura M, Slots J. Salivary enzymes. Origin and relationship to periodontal disease. J Periodont Res 1983;18:559-69.

123. Natali A, Toschi E, Baldeweg S, et al., clustering of insulin resistance with vascular dysfunction and low-grade inflammation in type 2 diabetes. Diabetes 2006;55:1133-40.

124. Nelson S, Laughon BE, Summer WR. Characterization of the pulmonary inflammatory response to an anaerobic bacterial challenge. Am Rev Respir Dis 1986;133:212-7.

125. Noack, Genco RJ, Trevisan M, Grossi S, Zambon JJ, De Nardin E.. Periodontal infection contribute to elevated systemic c-reactive protein level. J Periodontal 2001;72:1221-7.

126. Nonnenmacher, Stelzel M, Susin C, Sattler AM, Schaefer JR, Maisch B, Mutters R, Flores-de-Jacoby L. Periodontal microbiota in patients with coronary artery disease measured by real-time polymerase chain reaction: A case-control study. J Periodontol 2007;78:1724-30.

127. Offenbacher S. Elevated human IgM suggests in utero exposures to periodontal pathogens. J Dent Res 1999;78:2191.

128. Offenbacher S, Champagne CM, Madianos PN, Lieff S, Murtha AP, Beck JD,. Periodontal medicine: emerging concepts in pregnancy outcomes. J Int Acad Periodontol. 2000 Jan;2(1):9-13.

129. Offenbacher S, Jared HL, O'Reilly PG, Wells SR, Salvi GE, Lawrence HP, Socransky SS, Beck JD. Potential pathogenic mechanisms of periodontitis associated pregnancy complications. Ann Periodontal 1998;3:233-50.

130. Offenbacher S, Katz V, Fertik G, Collins J, Boyd D, Maynor G, McKaig R, Beck J. Periodontal disease as a possible risk factor for preterm low birth weight J Periodontal 1996:67(suppl):1103-13.

131. Offenbacher S, Lieff S, Boggess KA, Murtha AP, Madianos PN, Champagne CM, McKaig RG, Jared HL, Mauriello SM, Auten RL Jr, Herbert WN, Beck JD. Maternal periodontitis and prematurity. Part 1: Obstetric outcome of prematurity and growth restriction. Ann Periodontal 2001;6:164-74.

132. Offenbacher S, Salvi GE- Induction of prostaglandin release from macrophages by bacterial endotoxin. Clin Infect Dis. 1999 Mar;28(3):505-13.

133. Okuda K, Ebihara Y.Relationships between chronic oral infectious diseases and systemic diseases. Bull Tokyo Dent Coll. 1998 Aug;39(3):165-74.

134. Okuda K, Ishihara K, Nakagawa T, Hirayama A, Inayama Y, Okuda K. Detection of Treponema denticola in atherosclerotic lesions. J Clin Microbiol 2001;39:1114-7.

135. Okuda K, Kato T, Ishihara K. Involvement of periodontopathic biofilm in vascular diseases. Oral Dis 2004;10:5-12.

136. Paige et.al The pathology of periodontal diseases may effect systemic diseases: inversion of a paradigm. Ann Periodontal 1998;3:108-20.

137. Patricia A, Mario T, Auro N, Maria C, Flavia A, Sergio A, Glauce L, Arthur B, Sergio L, Daniela B, and Marcio F, Effects of periodontal therapy on glycemic control and inflammatory markers. J Periodontal 2008:79:774-83.

138. Persson GR. Chronic periodontitis, a significant relationship with acute myocardial infarction. Eur Heart J 2003;24:2108-15.

139. Persson GR, Pettersson T, Ohlsson O, Renvert S. High-sensitivity serum c-reactive protein levels in subjects with or without myocardial infarction or periodontitis. J Clin Periodontal 2005;32:219-24.

140. Phillip Bonner Offenbacher S The link between periodontal disease and systemic health: a scientific update. Interview by, Dent Today. 1999 Jul;18(7):88-90.

141. Pickup JC, Crook MA. Is type 2 diabetes mellitus a disease of the innate immune system ? Diabetology 1998;41:1241-8.

142. Plomgaard P, Bouzakri K, Krogh-Madsen R, Zierath JR, Pedersen BK. Tumor necrosis factor-alpha induces skeletal muscle insulin resistance in healthy human subjects via inhibition of substrate 160 phosphorylation. Diabetes 2005;54:2939-45.

143. Pontes Andersen CC, Buschard K, Flyvbjerg A, Stoltze K, Holmstrup P. Periodontitis deteriorates metabolic control in type 2 diabetic Goto-Kakizaki rats. 2006 Mar;77(3):350-6.

144. Preston AJ, Gosney MA, Noon S, Martin MV. Oral flora of elderly patients following acute medical admission. Gerodontol 1999;45:49-52.

145. Pucar A, Milasin J, Lekovic V, Vukadinovic M, Ristic M, Putnik S, Kenney EB. Correlation between atherosclerosis and periodontal putative pathogenic bacterial infections in coronary and internal mammary arteries. J Periodontal 2007;78:677-82.

146. Pucar A. Correlation between atherosclerosis and periodontal putative pathogenic bacteria infections in coronary and internal mammary arteries. J Periodontal 2007;78;677-82.

147. Pugin J, Auckenthaler R, Lew DP. Oropharyngeal decontamination decreases incidence of ventilator-associated pneumonia. A randomized, placebo-controlled, doubled-blinded clinical trial. JAMA 1991;265:2704-10.

148. Pussinen PJ, Nyyssönen K, Alfthan G, Salonen R, Laukkanen JA, Salonen JT. Serum antibody levels to Actinobacillus actinomycetemcomitans predict the risk for coronary heart disease. Arterioscler Thromb Vasc Biol 2005;25:833-38.

149. Quinn MO, Miller VE, Increased salivary exoglycosidase activity during critical illness. Am J Resp Crit Care Med 1994;150:179-83.

150. Rams TE, Babalola O, Slots J, Subgingival occurrence of enteric rods, yeasts and staphylococci after systemic doxycycline therapy. Oral Microbial Immunal 1900;5:166-8.

151. Reddy K, Wilson M, Nair S, Pole S, Henderson B. Comparsion of the pro-inflammatory cytokine-stimulating activity of the surface-associated proteins of periodontopathogenic bacteria. J Periodont Res 1996;31:120-30.

152. Reddy MS, Murphy TF, Faden HS, Bernstein JM. Middle ear mucin glycoprotein:purification and interaction with nontypable haemophilus influenza and moraxella catarrhalis. Otolaryngol Head Neck Surg 1997;116:175-80.

153. Renvert S. Destructive periodontal disease in relation to diabetes mellitus, cardiovascular diseases, osteoporosis and respiratory diseases. Oral Health Prev Dent 2003;1:341-57.

154. Rivera DL, Olister SM, Liu X, Thompson JH, Zhang XJ, Pennline K, Azuero R, Clark DA, Miller MJ. Interleukin-10 attenuates experimental fetal growth restriction and demise. FASEB J. 1998 Feb;12(2):189-97.

155. Roberts FA, Houston LS, Lukehart SA, Mancl LA, Persson GR, Page RC. A Periodontitis vaccine decreases local prostaglandin E2 levels in a primate model. Infect Immun;2004:1166-8.

156. Robinson WG Jr, Kador PF, Kinoshita JH. Retinal capillaries: Basement membrane thickening by galactosemia prevented with aldose reductase inhibitor. Science 1983;221:1177-79.

157. Rok S, Uros S. Periodontal disease and diabetes metabolic control: A full mouth disinfection approach. Jour of the Inter Acad of Periodontal 2006;8:61-6.

158. Roles of porphyrins and host iron transport proteins in regulation of growth of Porphyromonas gingivalis W50.Bramanti TE, Holt SC.J Bacteriol. 1991 Nov;173(22):7330-9.

159. Romero BC, Chiquito CS, Elejalde LE, Bernardoni CB.. Relationship between periodontal disease in pregnant women and the nutritional condition of their newborns. J Periodontal 2002;73:1177-83.

160. Rossomando EF, White L. A novel method for the detection of the TNF-α in gingival crevicular fluid. J Periodontal 1993;64:445-49.

161. Rush B. An account of the core of several diseases by the extraction of decayed teeth. 1818:5th edn.pp.197-201.

162. Russell SL, Boylen RJ, Kaslick RS, Scannapieco FA. Respiratory pathogens colonization of the dental plaque of institutionalized elders. Spec Care Dent 1999;19-1-7.

163. Salvi GE, Collins JG, Yalda B, Arnold RR, Lang NP, Offenbacher S. Monocytic TNF-α secretion patterns in IDDM patients with periodontal diseases. J Invest Dermatol 2004;123:87-92.

164. Sammalkorpi K, Glucose intolerance in acute infections. J Intern Med 1989;225:15-19.

165. Saremi A, Nelson RG, Tulloch-Reid M, Hanson RL, Sievers ML, Taylor GW, Shlossman M, Bennett PH, Genco R, Knowler WC. Periodontal disease and mortality in type 2 diabetes. Diabetes Care 2005;28:27-32.

166. Scannapieco A, Alex W. Potential association between chronic respiratory disease and periodontal disease: Analysis of the national health and nutritional examination survey III. J Periodontal 2001;72:50-56.

167. Scannapieco FA, Mylotte JM. Relationships between periodontal diseases and bacterial pneumonia. J Periodontal 1996;67(suppl):1114-12.

168. Scannapieco FA, Papandonatos GD, Dunford RG. Association between oral conditions and respiratory disease in a national sample survey population. Ann Periodontal 1998;3:251-6.

169. Scannapieco FA, Stewart EM, Mylotte JM. Colonization of dental plaque by respiratory pathogens in medical intensive care patients. Crit Care Med 1992;20:740-5.

170. Scannapieco FA,. Role of oral bacteria in respiratory infection. J Periodontal 1999;70:793-802.

171. Seinost G, Wimmer G, Skerget M, Thaller E, Brodmann M, Gasser R, Bratschko RO, Pilger E. Periodontal treatment improves endothelial dysfunction in patients with severe periodontitis. Am Heart J 2005: 149: 1050-4.

172. Sinclair DG, Evans TW. Nosocomial pneumonia in the intensive care unit. Br J Hosp Med 1994;51:177-80.

173. Slots J, Genco RJ. Black-pigmented bacteroides spieces, Capnocytophaga species & Actinobacillus actinomycetemcomitans in humans periodontal disease: virulence factor in colonization, survival and tissue destruction. J Dent Res 63,412-21.

174. Slots J, Rams TE. Microbiology of periodontal disease. Book Inc;1992:425-43.

175. Smith DD. Systemic infection due to natural teeth conditions. Dent Dig 1903:9:397-412.

176. Socransky SS, Haffajee AD - The bacterial etiology of destructive periodontal disease: current concepts.. J Periodontol. 1992 Apr;63(4 Suppl):322-31.

177. Soskoline WA. Epidemiological and clinical aspects of periodontal diseases in diabetes. Ann Periodontal 1998;3:3-12.

178. Steadman FStJ. Oral sepsis as a predisposing cause of cancer. Br Dent J 1914:35:664-52.

179. Stelzel, Conrads G, Pankuweit S, Maisch B, Vogt S, Moosdorf R, Flores-de-Jacoby L. Detection of Porphyromonas gingivalis DNA in aortic by PCR. J Periodontal 2002;73:868-70.

180. Stewart JE, Wager KA, Friedlander AH, Zadeh HH. The effect of periodontal treatment on glycemic control in patients with type 2 diabetes mellitus. 2001 Apr;28(4):306-10.

181. Taylor GW, Burt BA, Becker MP, et al., Severe periodontitis and risk for poor glycemic control in patients with non-insulin-dependent diabetes mellitus. J Periodontal 1996;67:1085-93.

182. Taylor SH. Congestive heart failure. Towards a comprehensive treatment.Eur Heart J.1996;4;17 suppl B:43-56.

183. Terpenning M, Bretz W, Lopatin D, Langmore S, Dominguez B, Loesche W. Bacterial colonization of saliva and plaque in the elderly. Clin Infect Dis 1993;16(Suppl.40:S314-S16).

184. Terrone DA, Rinehart BK, Granger JP, Barrilleaux PS, Martin JN Jr, Bennett WA.Interleukin-10 administration and bacterial endotoxin-induced preterm birth in a rat model. Obstet Gynecol 2001;98:476-80.

185. Tervonen T, Knuuttila M, Pohjamo L, Nurkkala H. Immediate response to nonsurgical periodontal treatment in subjects with diabetes mellitus. J Clin Periodontal 1991;18:65-8.

186. Tervonen T, Oliver RC. Long-term control of diabetes mellitus and periodontitis. J Clin Periodontol 20, 432-5.

187. Thorstensson H, Kuylenstierna J, Hugoson A. Medical status and complications in relation to periodontal disease experience in insulin-dependent diabetics. J Clin Periodontal 1996;23:194-202.

188. Toews GB, Nosocomial pneumonia.Am J Med Sci 1986;291:355-67.

189. Torres A, Docra J, Zalacain R et.al. Community-acquired pneumonia in chronic obstructive pulmonary disease: a Spanish multicenter study. Am J Resp Crit Care Med 1996;154:1456-61.

190. Trelor DM, Stechmiller JK. Use of a clinical assessment tool for orally intubated patients. Am J Crit Care 1995;4:355-60.

191. Tunstall-Pedoe H, Vanuzzo D, Hobbs M, Mähönen M, Cepaitis Z, Kuulasmaa K, Keil u..Estimation of contribution of changes in classic risk factors to trends in coronary-event rate across the WHO MONICA Project populations. Lancet 2000;355:675-87.

192. Tuter, Kurtis B, Serdar M. Evaluation of gingival crevicular fluid and serum levels of high- sensitivity c-reactive protein in chronic periodontitis patients with or without coronary artery disease. J Periodontal 2007;78:2319-24.

193. Vercelotti GM. Potential role of viruses in thrombosis and atherosclerosis. Trends Cardiovasc Med 1995;5:128-33.

194. Villar J, Gülmezoglu AM, de Onis M.-Nutritional and antimicrobial interventions to prevent preterm birth: an overview of randomized controlled trials. Obstet Gynecol Surv. 1998 Sep;53(9):575-85.

195. Wanng X, Yue TL, Ohlstein EH, Sung CP, Feuerstein GZ.Interferon-inducible protein-10 involves vascular smooth muscle cell migration, proliferation, and inflammatory response. J Biol Chem 1996; 271: 24286-293.

196. Watanakunakorn, Pantelakis J. Alpha-hemolytic streptococcal bacteremia: A review of 203 episodes during 1980–1991. Scand J Infect Dis 1993; 25: 403–8.

197. Weinmeister KD, Dal Nogare AR. Buccal cell carbohydrates are altered during critical illness. Am J Resp Crit Care Med 1994; 150: 131-4.

198. Williams NB, Burket LW. Focal infection-a review. Philadelphia Med 1951:46:1509.

199. Wlliams RC Jr, Mahan CJ. Periodontal disease and diabetes in young adults. JAMA 1960;172;776-8.

200. Woods DE, Straus DC, Johanson WG, Bass JA. Role of fibronectin in the prevention of adherence of pseudomonas aeruginosa to buccal cells. J Inf Dis 1981;143:784-90.

201. Yeo. Campylobacter rector mediates growth restriction in pregnant mice. J Periodontal 2005;76:551-7.

202. Ylostalo, Järvelin MR, Laitinen J, Knuuttila ML. Gingivitis, dental caries and tooth loss: risk factors for cardiovascular diseases or indicators of elevated health risks. J Clin Periodontal 2006:33;92-101.

203. Yoneyama T, Fukuda H, et al., Oral hygiene reduces respiratory infections in elderly bed-bound nursing home patients. Arch Gerontol 1996;22;11-9.

204. Yoon BH, Romero R, Kim CJ, Koo JN, Choe G, Syn HC, Chi JG. High expression of tumor necrosis factor-alpha and interleukin-6 in periventricular leukomalacia. Am J Obstet Gynecol. 1997 Aug;177(2):406-11.

205. Yoshihiro I, Fusanori N, Masatsugu N, Hikaru S, Kenichi S, Hirofumi M, Tetsuya F, Takao T, Masahiro I & Yoji M, The effect of antimicrobial periodontal treatment on circulating tumor necrosis factor-alpha and glycated hemoglobin level in patients with type 2 diabetes. J Periodontal 2001;72:774-8.

206. Yuan A, Luh KT, Yang PC. Actinobacillis actinomycetemcomitans pneumonia with possible septic embolization. Chest 1994;105:646.

207. Zabbon. Identification of periodontal pathogens in atheromatous plaques. J Dent Res 1997;76(spec.Issue):408(Abstr.3159).

208. Zain B. Role for periodontitis in the progression of lipid deposition in an animal model. Infect Immun 2003;71:6012-8.

209. Zambon JJ, Nakamura M, Slots J. Effects of periodontal therapy on salivary enzyme activity. J Periodont Res 1985;20:652-9.

210. Zaremba J. Evaluation of the incidence of periodontitis-associated bacteria in the atherosclerotic plaque of coronary blood vessels. J Periodontal 2007;78:322-7.

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Periodontal Medicine

About the Book

This text book explores the complex relationship between the periodontium and systemic diseases. The book is prepared with the objective of keeping the mind to the benefits of postgraduate dental students. Topic covered include cardiovascular, respiratory disease, diabetes and pregnancy. A methodological approach and simplicity in language has been the most important objective of the edition.

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