

Review Paper

IMPACT OF CHRONIC PERIODONTITIS ON SYSTEMIC CONDITIONS: A REVIEW

ABSTRACT

The oral cavity might well be thought of as the window of the human body due to the extent of the inflammatory burden caused by periodontal disease. This can influence systemic diseases with a similar inflammatory pathology and vice versa, raising the relevance regarding periodontal and systemic health affecting each other. The interrelationship between periodontal disease and systemic health has been a matter of debate since ancient times. A theory of focal infection states that the oral pathogens had the capability to either directly enter or release their toxic products into the systemic circulation. Recent evidence reveals that we need to change our thought about the etiology and pathogenesis of periodontal disease. Although bacteria are a necessary factor in the equation, the reaction of the host's immuno-inflammatory system is responsible for most of the destruction found in periodontal disease. Thus, it makes sense that a number of environmental and acquired factors may modify a patient's risk of developing periodontal disease. Since oral health has a significant influence on the final prognosis of a number of systemic disorders, it is essential that we understand the underlying pathophysiology linking oral health to systemic health.

Keywords: Cardiovascular systemic health periodontal disease periodontitis preterm delivery

INTRODUCTION

Offenbacher [1] introduced the term "Periodontal Medicine" to be a broad term defining a rapidly emerging branch of periodontology focusing on the health. New data are emerging that establishes a strong relationship between periodontal health or disease and systemic health or disease. Today the unifying concept of periodontal medicine states that periodontal infection results in a significant chronic inflammatory burden at the systemic level.

The various modern pathogenic concepts of systemic disorders include autointoxication, focal infection, psychosomatic disease, and autoimmunity. "Miller's focal infection theory" explains the role of oral pathogens in systemic disease [2,3]. The field of periodontal medicine has evolved into a significant oral and systemic health care media, since its inception in 1996 during the world workshop of periodontology [4].

HISTORY

Egyptian medicine had the notion that extracting tooth would aid in improving the overall health of an individual. The oldest available medical papyri of the middle dynasty belonging to 2100 BC mentions an association between the diseases in a women's reproductive system and poor dental status. Even Hippocrates proposed that extracting infected tooth could cure rheumatism.

"The Natural History of the Human Teeth" written by John Hunter (1778) made a controversial introductory note, acknowledging the unique nature of diseases of the tooth, and emphasized on its impact on systemic disorders. His proposal was disregarded and any further attempt to interrelate oral disease to systemic manifestations were ignored.

Robert Koch (1876) proposed the “Germ theory” based on the results of numerous studies revealing the role of microorganisms in causing infectious diseases. Miller [3] studied the relationship between oral bacteria and systemic diseases. He wrote a series of articles titled “The Human Mouth as a Focus of Infection” linking a number of systemic disorders including pulmonary diseases, brain abscesses, and gastric problems with oral microorganisms and their products.

Based on the findings of Miller on focal infections, William Hunter (1900) a physician, investigated the prevalence, extent, and treatment modalities of oral infection-induced medical complications. Hunter introduced the term “oral sepsis.” He defined the term oral sepsis to emphasize that oral sepsis represents a foci of infection which may be due to tooth decay or other oral infections like gingivitis. He also emphasized the importance of recognizing the role of specific organisms like staphylococcal and streptococcal species which accounts for the majority of oral infection. William Hunter (1900) demonstrated the haematogenous spread of oral bacteria and their products causing numerous systemic illness including endocarditis, nephritis, empyema, cholecystitis, perinephric abscess, and anaemia.

The term “oral sepsis” was replaced with “focal infection.” Frank Billings, (1911) a physician-defined the probable sources of infection in the human body. Billings and associates stated that systemic diseases including chronic arthritis and myositis may occur as a result of a primary or secondary focal alveolar infection [5]

Kopeloff and many other physicians of the 1930’s questioned the accuracy of relating all systemic disorders with questionable cause to oral infection. [5]

Appleton 1944 [6] proposed three pathways for dental infection resulting in systemic dissemination.

1. Metastasis of the infectious organism by active transport in blood vessels or lymphatic channels
2. Passive diffusion into the lymph or blood enabling the bacterial products to reach the most remote areas of the body
3. The products of bacterial autolysis may in turn be a potential allergen disseminating into the blood or lymph.

Following Appleton, Miller proposed the possible routes of infection from periodontal pockets:

- a. Blood and lymph
- b. Direct extensions of the tissue
- c. Swallowing and aspiration of infective material enabling passage through gastrointestinal and pulmonary tracts respectively

Miller also emphasized the importance of the presence of a well-established lymphatic system draining gingiva and adjacent soft tissues. Spread of infectious agent or its toxic products to regional lymph nodes was considered a likely possibility

FOCI OF INFECTION

Mattila et al [7] reported an increased prevalence of acute myocardial infarction in patients with poor oral status. They suggested oral foci to have an independent impact on the initiation of myocardial infarction in the absence of other risk factors for cardiovascular disease.

Haffajee and Socransky [8] estimated the subgingival biofilms to accommodate more than 700 microbial colonies. Introduction of microarray techniques allowed us to sequence about 600 bacterial species from an individual biofilm.

World workshop of Periodontology (1996) introduced the term “periodontal medicine”. The purpose of creating this new discipline was to evaluate the possible role of periodontal diseases on the initiation and progression of cardiovascular diseases. Multiple studies have associated the presence of high inflammatory markers, intima-media thickness, uncontrolled glycemic level in diabetes, and cholesterol level alterations with periodontal disease.

Environmental and acquired risk factors affect the onset, rate of progression and severity of periodontal disease as well as the response to therapy. Risk factor is defined as “an aspect of personal behaviour or lifestyle, an environmental exposure, or an inherited characteristic, which on the basis of epidemiologic evidence is known to be associated with a health related condition. Although the risk factor may not be a proven cause of a particular disease, its presence implies a direct increase in the probability of the disease occurring.

Based on clinical research, age, genetics, smoking and diabetes mellitus are known as the risk factors for periodontal disease. Psychosocial stress and osteoporosis are also considered less likely, but still potential risk factors. The evidence for each of these risk factors is outlined below.

Age

The prevalence of periodontal disease increases with age [8,9]. It is unclear whether becoming older is related to increasing attachment loss or if the worsening periodontal status is related to the consequences of aging. Although aging is associated with metabolic changes, it is not directly linked with periodontal attachment loss. It is found that the rate of periodontal destruction increases after the age of 70 years, up to that age, the rate of attachment loss remains the same [10].

Genetics

Various sources suggest genetics play a significant role in certain periodontal diseases. Early-onset periodontal diseases like prepubertal, juvenile and rapidly progressing periodontal disease have a strong genetic component [11]. Recently, it has been found that a combination of 2 polymorphisms in the interleukin-1 (IL-1) gene is associated with a severe form of adult periodontitis [12]. Studies shows that a genotype-positive patient is around 20 times more likely to develop advanced adult periodontitis beyond 40 years of age than a genotype-negative patient [13].

Smoking

Various studies have shown that smoking is strongly associated with periodontitis. The majority of tooth loss in adults aged between 19-40 is associated with smoking more than 15 cigarettes a day [14]. A linear dose-response relation between smoking and bone loss has also been shown. Grossi et al [15] found that, compared with a non-smoker, a light smoker was 2 times more likely to have alveolar bone loss.

The biologic basis for smoking as a risk factor for periodontal disease is that smoking inhibits neutrophil functioning saliva as well as in connective tissues. [16] It suppresses immunoglobulin G2 antibody response and enhances the release of interleukin-1 beta (IL-1 β), which affects osteoblast function[17]Along with that, it constricts the gingival blood vessels, which accounts, for the lack of bleeding on probing found in most smokers. Periodontal therapy, both surgical and nonsurgical, is less

likely to be effective in smokers and periodontal disease is more likely to recur when compared to non-smokers. [18,19]

RELATIONSHIP BETWEEN PERIODONTAL DISEASE AND SYSTEMIC DISEASES

Based on epidemiological studies it has been shown that there is an association between periodontal infection, with particular emphasis on chronic periodontitis, and a number of clinically important systemic diseases [20-24]. These include cardiovascular diseases, respiratory diseases, diabetes, adverse pregnancy outcomes, Alzheimer's disease, and other systemic conditions. However, a direct role of periodontal infection in the development and or/progression of systemic diseases has not yet established.

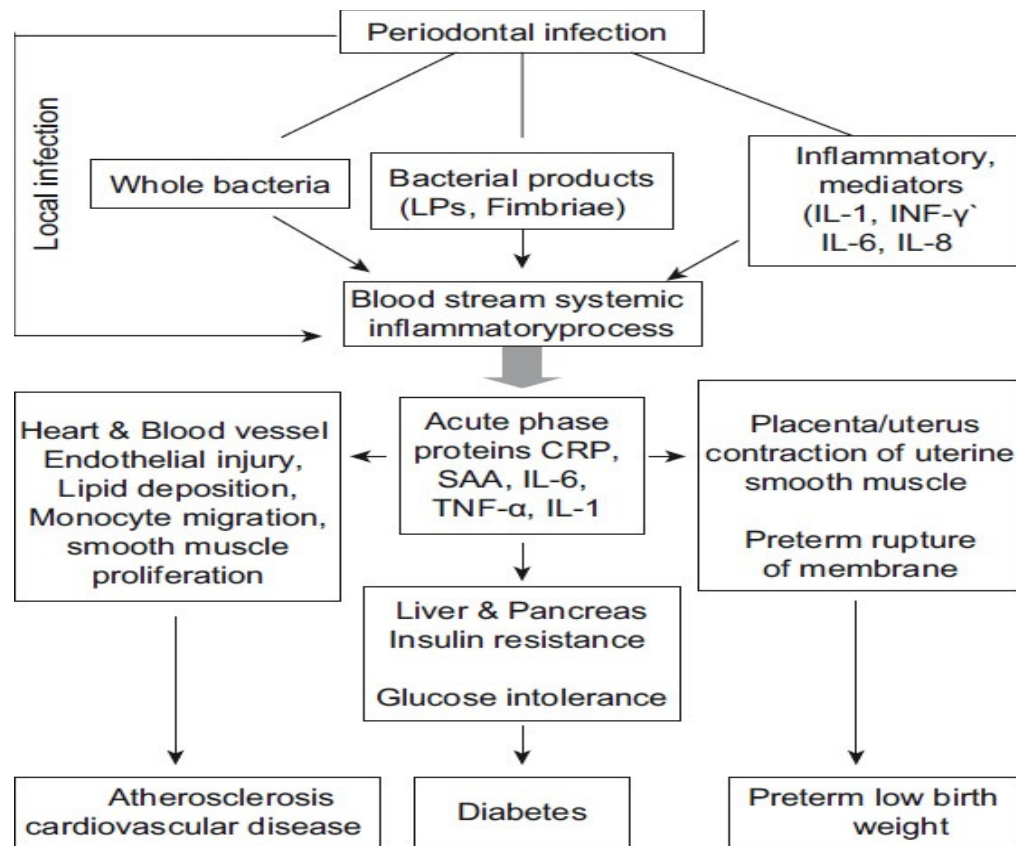


Figure 1: Periodontal infection and systemic conditions – Potential linkage and possible pathogenic mechanisms

MECHANISMS CONNECTING PERIODONTAL AND SYSTEMIC DISEASES

Numerous hypotheses have been proposed explaining the mechanism underlying periodontal disease and systemic diseases

Paquette et al and Seymour et al [25],[26] proposed that

1. Oral infection and systemic diseases show common susceptibility through shared risk factors: This common susceptibility can be mediated through genetic or environmental factors such as age, smoking, and socioeconomic status. Based on this hypotheses, it was proposed that periodontal disease is associated with systemic diseases, but the relationship is not causal. Periodontal disease by

itself will not initiate any systemic disease. It only aggravates the host immune response of the individual there by exaggerating the severity of the systemic disease.

2. Systemic inflammation with high levels of circulating inflammatory mediators in response to the local infection or circulating bacteria like periodontal infection and immune responses may play a causal role in systemic disease.

3. Systemic dissemination of oral bacteria or their products due to periodontal infection causes bacteremia and endotoxemias which may subsequently play a causal role in systemic diseases.

4. Cross-reactivity between bacterial and host heat-shock proteins results in an autoimmune response that may contribute to the progression or development of systemic diseases.

Periodontal disease and coronary heart disease/atherosclerosis and stroke

Cardiac diseases include congestive heart failure, coronary artery disease which includes atherosclerosis and myocardial infarction, valvular heart disease, and stroke. Of all these, atherosclerosis is considered as a major component of cardiovascular diseases, which is characterized by the deposition of atherosclerotic plaques on the innermost layer of walls of large and medium-sized arteries. Final outcomes associated with atherosclerosis include coronary thrombosis, myocardial infarction, and stroke. Several mechanisms that could explain this association have been studied. The host response to the presence of periodontal pathogens may induce the production of inflammatory mediators like C-reactive protein, tumour necrosis factor (TNF)- α , prostaglandin E₂ (PGE₂), interleukin (IL-1 β), and IL-6, which can accelerate the progression of pre-existing atherosclerotic plaques and can be related to a number of adverse cardiovascular events. Also, several studies have shown the ability of periodontal pathogens to induce platelet aggregation and the formation of atheroma.[27,28]

Myocardial infarction (MI) is associated with acute systemic bacterial and viral infections. A systematic review of Scannapieco et al. [29] emphasized the association between periodontal disease and cardiovascular disease. The authors concluded that periodontal disease may be strongly associated with atherosclerosis, MI, and cardiovascular events. Janket et al., 2003, in their cross-sectional studies compared the patients with acute MI or confirmed coronary heart disease, with controls. MI patients had significantly severe periodontitis than the controls. The association between oral health and MI was independent of known risk factors for heart disease such as age, cholesterol levels, hypertension, diabetes, and smoking. Cross-sectional studies thus suggest a possible link between periodontal disease and coronary heart disease

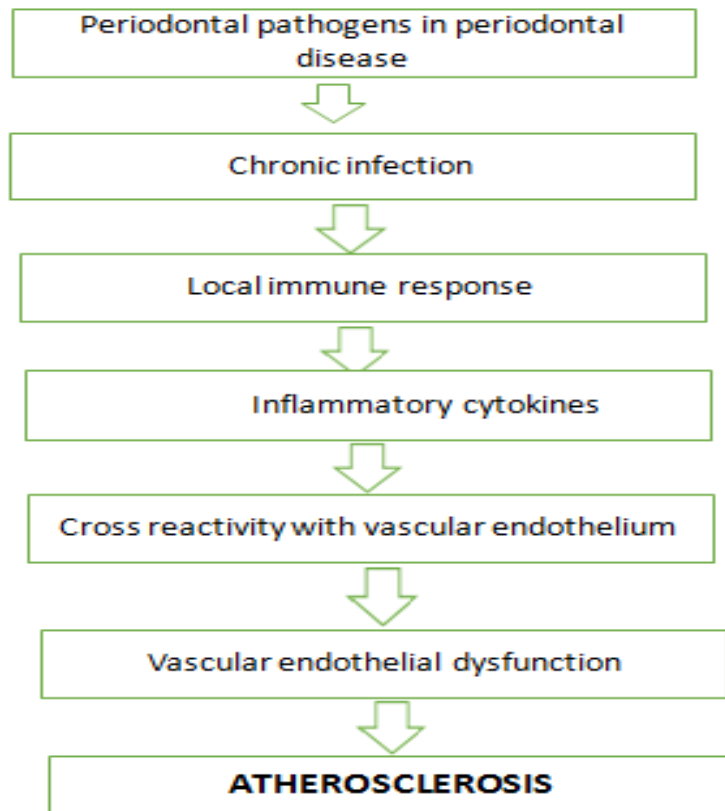


Figure 2: Possible pathogenic mechanism between periodontal disease and atherosclerosis

Mattila [30] and his co-workers in Finland conducted two separate case control studies totalling 100 patients with acute myocardial infarction and they compared these patients with 102 control subjects selected from the community subjects with evidence of oral infection were 30% more likely to present with myocardial infarction as against subjects without oral infections.

Genco and co-workers (1972) investigated the association between periodontal infections and risk of CVD among Native Americans of Gila River Indian community. Among all age groups alveolar bone level was predictive for coronary heart disease, but did not remain significant in a multivariate analysis [31]

Periodontal disease and diabetes mellitus

Diabetes is a group of metabolic diseases characterized by hyper glycemia and results from either a deficiency in the secretion of insulin and/or impaired insulin action[32].The interrelationship between diabetes and periodontal disease is established through a number of pathways.

One of the mechanisms to explain the relationship between diabetes mellitus and periodontal disease suggests that the presence of periodontal disease may induce or perpetuate a state of chronic systemic inflammation, by the increase in the C-reactive protein, IL-6, IL-1, and fibrinogen levels found in individuals with periodontitis. Periodontal infection may elevate the state of systemic inflammation and increases the resistance to insulin, because the inflammatory process induces this resistance. Furthermore, it may induce increased levels of IL-6 and TNF- α , which is similar to obesity, inducing or exacerbating the resistance to insulin. [33] Diabetes increases the risk for and severity of

periodontal diseases and now periodontal disease is considered as the sixth complication of diabetes.[33]

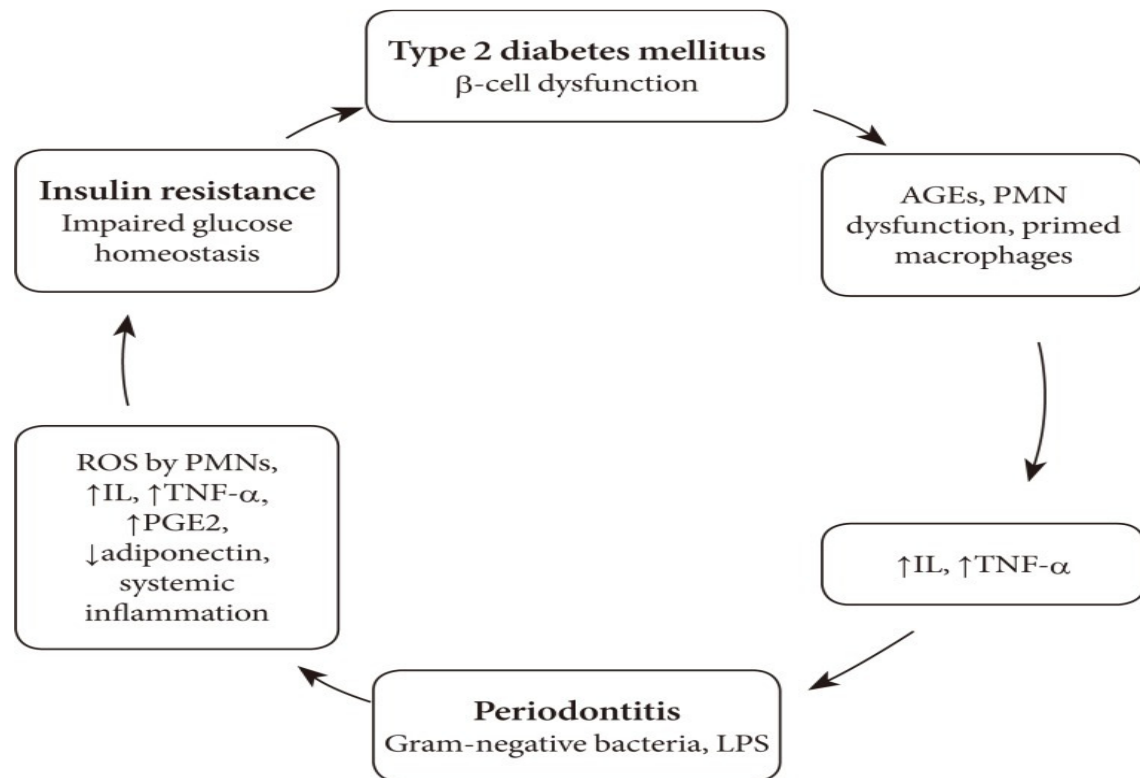


Figure 3: relationship between diabetes and periodontitis

The synergism between diabetes and periodontal disease has been demonstrated in a number of studies. Various studies done by O'Connell et al, Engebretson et al and Simpson et al [34,35,36] have shown that effective periodontal treatment can improve some complications of diabetes, especially hyperglycemia, and that severe periodontitis is associated with poor blood sugar control. Periodontal treatment improves glycemic control, especially in individuals with type 2 diabetes, and its association with low glycated haemoglobin levels has been demonstrated.

Taylor et al [37] conducted a longitudinal study in patients with type 2 or non-insulin dependent diabetes with severe periodontitis and proposed that severe periodontitis is associated with significant worsening of glycemic control over time. Mealey et al [38] proposed that periodontal treatment designed to decrease the bacterial insult and reduction of inflammation might restore insulin sensitivity over time, resulting in improved metabolic control.

The study of Mealey BL, Klokkevold [39] found that people with diabetes mellitus are 15 times more likely to be edentulous than people without the disease. Both type 1 or insulin dependent and type 2 or non insulin dependent have the same effect. The likelihood of periodontal disease increases when diabetic control is poor. People with well-controlled diabetes, with good oral hygiene and on a regular maintenance schedule have the same chance of developing severe periodontitis as people without diabetes. The mechanism is multifactorial. The small blood vessels of people with diabetes have thickened basement membranes, which will lead to reduction in transport across the vessel walls. There is a reduction in collagen production by gingival and periodontal fibroblasts. In addition, high

levels of pro inflammatory mediators produced in response to endotoxin from gram negative bacteria also leads to increase in collagen breakdown.

Periodontal disease and pregnancy outcome

It has been observed that oral infections may increase the risk of low birth weight (LBW). Low birth weight is defined, according to the World Health Organisation in 1976, as a birth weight lower than 2500g. The etiology of preterm birth (PB) is multi factorial, but inflammation is the common pathway which leads to uterine contractions and cervical changes with or without premature rupture of membranes. The main cause of low birth weight deliveries is premature rupture of membrane (PROM) and preterm delivery. [40] Periodontal infection and inflammation result in increased levels of toxic products (lipopolysaccharides) from bacteria and also inflammatory mediators released from the host, especially prostaglandins, tumour necrosis factor alpha (TNF- α), interleukins-1 (IL-1) and IL-6. This induces placental and systemic inflammatory response resulting in PROM and preterm delivery [41] Inflammation associated with pre term birth can be mainly attributable to intrauterine infection and bacterial vaginosis that accounts for up to 40% of the cases of spontaneous preterm labor and pre term birth. There is also a causal relationship between bacteria and pre term birth and the presence of significantly higher levels of pro inflammatory cytokines and prostaglandins in the amniotic fluid [42]. Pre term birth can be due to the haematogenous dissemination of inflammatory products from a periodontal infection. Metastatic injury from the effects of circulating oral microbial toxins, eg: lipopolysaccharide, which is continuously shed from periodontal gram-negative rods during growth, and when introduced into the host, gives rise to a large number of pathological manifestations [43] and metastatic inflammation caused by immunological injury induced by oral microorganisms.

During the second trimester of pregnancy, the proportion of Gram-negative anaerobic bacteria in dental plaque increases in respect to aerobic bacteria. [44] Periodontal organisms *Porphyromonas gingivalis* (*P.gingivalis*), *Fusobacterium nucleatum*, *Capnocytophaga* species and *Campylobacter rectus* have been isolated from the amniotic fluid of women with PTLBW deliveries. In a cross-sectional study, women with low birth weight infants had higher levels of *Actinobacillus actinomycetemcomitans*, *Bacteroides forsythus*, *P gingivalis* and *Treponema denticola* when compared with normal birth weight infants. [45]

The high prevalence of elevated fetal IgM to *Campylobacter rectus* among premature infants raises the possibility that this specific maternal oral pathogen may serve as a primary fetal infectious agent, eliciting prematurity and also restricting fetal growth [46]. An animal study concluded that *P.gingivalis* infection during pregnancy increased maternal tumor necrosis factor alpha, restricted fetal growth and also activated maternal immune and inflammatory responses [47] Increased levels of *Actinomyces naeslundii* genospecies and *Lactobacillus casei* levels were seen in low birth weight infants, which can be used as predictors of adverse pregnancy outcomes. [48] The identification of modifiable risk factors of Pre term low birth weight deliveries is of utmost importance. Among the various confirmed risk factors, only two can change smoking and alcohol. [49]

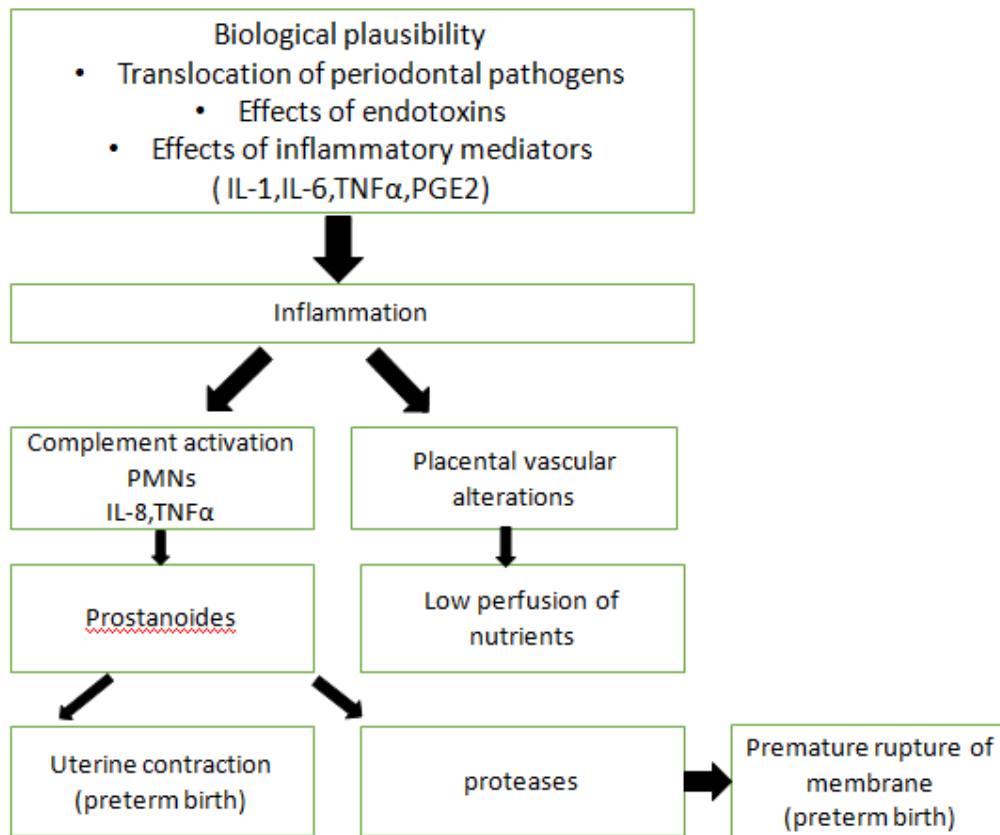


Figure 4: Potential pathogenic mechanism of preterm low birth weight and periodontitis

Periodontal disease and respiratory infections

Respiratory diseases are the term for diseases of the respiratory system, including lung, pleural cavity, bronchial tubes, trachea , and upper respiratory tract. They range from a common cold to life-threatening conditions such as bacterial pneumonia or chronic obstructive pulmonary disease (COPD), which are important causes of death worldwide.[50] There is increasing evidence that a poor oral health can predispose to respiratory diseases, especially in high-risk patients. The oral cavity is continuous with the trachea and may act as a portal for respiratory pathogen colonization. Dental plaque can be colonized by respiratory pathogens, which may be aspirated from the oropharynx into the upper airway and then reach the lower airway and adhere to the bronchial or alveolar epithelium. Scannapieco et al. [51] , conducted a systematic literature review to examine whether the rate of pneumonia in high-risk populations is reduced by interventions that improve oral hygiene. They found an association between periodontal disease and pneumonia and a potential association between periodontal disease and chronic obstructive pulmonary disease in several studies.

PERIODONTAL MEDICINE IN CLINICAL PRACTICE

The concept of periodontal diseases as localized entities affecting only the teeth and supporting structures should be corrected by now. Periodontal diseases may have wide-range of systemic effects, rather than being confined to the periodontium. In most individuals, these effects may be relatively negligible or at least not clinically evident. In susceptible individuals, however, the periodontal infection may act as a risk factor or may be involved in the basic pathogenic mechanisms of these conditions. Furthermore, periodontal disease may exacerbate existing systemic disorders. In the realm

of periodontal medicine, patient education must emphasize the nature of periodontal infections, the increased risk for systemic disease, and the biologically plausible role periodontal infection may play in systemic disease. Increased appreciation of the potential effects of periodontal infection on systemic health may result in increased patient demand for periodontal evaluation and dentists and medical professionals should join their hands in educating the patients regarding the same.

CONCLUSION

The emerging field of periodontal medicine offers new insights into the concept of chronic periodontitis as a condition interconnected with the whole human body. The potential link between periodontitis and systemic conditions is now the focus for a wide range of research around the world as evidenced by the emergence of a new branch, periodontal medicine. Medical specialists must recognize the emerging and increasing significance of this fact in comprehensive health care. Dental surgeons must improve their knowledge and clinical exposure to relevant systemic conditions in order to interact and relate meaningfully with their medical colleagues. Regular dental checkup is strongly advocated in the light of current knowledge. The oral healthcare professionals and the medical professionals have to correlate oral hygiene with patients systemic conditions for better prevention. It seems from the scientific evidence gathered so far that interventional periodontal care remains to be of utmost importance not only for oral health but for general health as well.

REFERENCE

1. Offenbacher S. Periodontal diseases: Pathogenesis. *Ann Periodontol* 1: 821-878; 1996
2. Vieira CL, Caramelli B. The history of dentistry and medicine relationship: Could the mouth finally return to the body? *Oral Dis* 2009; 15:538-46.
3. Miller WD. The human mouth as a focus of infection. *Dent Cosm* 1891; 33:689-713.
4. Oral health: Prevention is key. *Lancet* 2009; 373:1.
5. Kopeloff N. *Why Infections?* New York, London: Alfred Knopf; 1926.
6. Appleton JL. *Bacterial Infection with Special Reference to Dental Practice*. 3rd ed. Philadelphia: Lea and Febiger; 1944. p. 401-16
7. Mattila KJ, Nieminen MS, Valtonen VV, Rasi VP, Kesäniemi YA, Syrjälä SL, *et al.* Association between dental health and acute myocardial infarction. *BMJ* 1989; 298:779-81.
8. Haffajee AD, Socransky SS. Introduction to microbial aspects of periodontal biofilm communities, development and treatment. *Periodontol* 2006; 42:7-12.
9. Last J. *A dictionary of epidemiology*. New York: Oxford University Press, 1988
10. Grossi SG, Zambon JJ, Ho AW, Koch G, Dunford RG, Machtei EE and others. Assessment of risk for periodontal disease. I. Risk indicators for attachment loss. *J Periodontol* 1994; 65:260-7.
11. Hart TC. Genetic risk factors for early-onset periodontal diseases. *J Periodontol* 1996; 67:355-66.
12. Michalowicz BS, Aeppli D, Virag JG, Klump DG, Hinricas JE, Segal NL and others. Periodontal findings in adult twins. *J Periodontol* 1991; 62:293-9.
13. Kornman KS, Crane A, Wang HY, di Giovine FS, Newman MG, Pirk FW and others. The interleukin-1 genotype as a severity factor in adult periodontal disease. *J Clin Periodontol* 1997; 24:72-7.
14. Miller A, Brunelle J, Carlos J, Brown L, Löe H. *Oral health of United States adults: national findings*. Bethesda, MD: National Institute of Health, 1987
15. Machtei EE, Dunford R, Grossi SG, Genco RJ. Cumulative nature of periodontal attachment loss. *J Periodontal Res* 1994; 29:361-4.

16. Grossi SG, Genco RJ, Machtei EE, Ho AW, Kock G, Dunford R and others. Assessment of risk for periodontal disease. II. Risk indicators for alveolar bone loss. *J Periodontol* 1995; 66:23-9.
17. Bennet KR, Reade PC. Salivary immunoglobulin A levels in normal subjects, tobacco smokers, and patients with minor aphthous ulcerations. *Oral Surg Oral Med Oral Pathol* 1982; 53:461-5.
18. Payne JB, Johnson GK, Reinhardt RA, Dyer JK, Maze CA, Dunning DG. Nicotine effects on PGE2 and IL-1 beta release by LP treated human monocytes. *J Periodontal Res* 1996; 31:99-104.
19. Preber H, Bergström J. The effect of non-surgical treatment on periodontal pockets in smokers and non-smokers. *J Clin Periodontol* 1986; 13:319-23.
20. Preber H, Bergström J. Effect of cigarette smoking on periodontal healing following surgical therapy. *J Clin Periodontol* 1990; 17:324-8.
21. Grossi SG, Genco RJ. Periodontal disease and diabetes mellitus: A two-way relationship. *Ann Periodontol* 1998; 3:51-61.
22. Azarpazhooh A, Leake JL. Systematic review of the association between respiratory diseases and oral health. *J Periodontol* 2006; 77:1465-82.
23. Page RC. The pathobiology of periodontal disease may affect systemic disease: Inversion of a paradigm. *Ann Periodontol* 1998; 3:108-20.
24. Scannapieco FA. Position Paper, Periodontal disease as a potential risk factor for systemic diseases. *J Periodontol* 1998; 69:841-50.
25. Paquette DW. The periodontal infection-systemic disease link: a review of the truth or myth. *J Int Acad Periodontol* 2002; 4:101-9.
26. Seymour GJ, Ford PJ, Cullinan MP, Leishman S, Yamazaki K. Relationship between periodontal infections and systemic disease. *Clin Microbiol Infect* 2007; 13:3-10.
27. Weidlich P, Cimoës R, Pannuti CM, Oppermann RV. Association between periodontal diseases and systemic diseases. *Braz Oral Res* 2008; 22:32-43.
28. Herzberg MC, Weyer MW. Dental plaque, platelets, and cardiovascular diseases. *Ann Periodontol* 1998; 3:151-60.
29. Scannapieco FA, Bush RB, Paju S. Associations between periodontal disease and risk for atherosclerosis, cardiovascular disease, and stroke. A systematic review. *Ann Periodontol* 2003; 8:38-53.
30. Mattila KJ, Nieminen MS, Valtonen VV, Rasi VP, Kesäniemi YA, Syrjälä SL, *et al.* Association between dental health and acute myocardial infarction. *BMJ* 1989; 298:779-82.
31. Weidlich P, Cimoës R, Pannuti CM, Oppermann RV. Association between periodontal diseases and systemic diseases. *Braz Oral Res* 2008; 22:32-43.
32. Genco RJ, Chadda S, Grossi S, Dunford R, Taylor G, Knowler W, *et al.* Periodontal disease is a predictor of cardiovascular disease in a Native American population. *J Dent Res* 1997; 76:3158.
33. Mealey BL, Ocampo GL. Diabetes mellitus and periodontal disease. *Periodontol* 2000 2007; 44:127-53.
34. O'Connell PA, Taba M, Nomizo A, Foss Freitas MC, Suaid FA, Uyemura SA *et al.* Effects of periodontal therapy on glycemic control and inflammatory markers. *J Periodontol*. 2008; 79:774-83.
35. Engebretson SP, Hyman LG, Michalowicz BS, Schoenfeld ER, Gelato MC, Hou W, *et al.* The effect of nonsurgical periodontal therapy on hemoglobin A1c levels in persons with type 2 diabetes and chronic periodontitis: A randomized clinical trial. *JAMA*. 2013; 310:2523-32.
36. Simpson TC, Weldon JC, Worthington HV, Needleman I, Wild SH, Moles DR *et al.* Treatment of periodontal disease for glycaemic control in people with diabetes mellitus. *Cochrane Database Syst Rev*. 2015, 11.

37. Taylor GW. Bidirectional interrelationships between diabetes and periodontal diseases: An epidemiologic perspective. *Ann Periodontol*. 2001; 6:99–12.
38. Mealey BL, Oates TW. Diabetes mellitus and periodontal diseases. *J Periodontol*. 2006; 77:1289–93.
39. Mealey BL, Klokkevold PR. Periodontal medicine: Impact of periodontal infection on systemic health. In: Newman, Takei, Klokkevold, Ferman A, Editors. *Carranza: Clinical periodontology*, 10th ed, chapter 18, Philadelphia: WB Saunders and company, 2009. p. 312-29
40. Seppala B, Ainamo J. A site-by-site follow-up study on the effect of controlled versus poorly controlled insulin-dependent diabetes mellitus. *J Clin Periodontol* 1994;21:1615.
41. Tim McGaw. Periodontal Disease and Preterm Delivery of Low-Birth-Weight Infants. *J Can Dent Assoc*, 2002; 68(3): 165-169.
42. Li X, Kolltveit KM, Tronstad L, Olsen I. Systemic diseases caused by oral infection. *Clin Microbiol Rev.*, 2000; 13(4): 547-558
43. 44. Gibbs RS. The relationship between infection and adverse pregnancy outcomes: an overview. *Ann Periodontol*, 2001; 6(1): 153-163. 423
44. 46. Thoden van Velzen SK, Abraham-Inpijn L, Moorer WR. Plaque and systemic 426 disease: a reappraisal of the focal infection concept. *J. Clin. Periodontol*, 1984; 11(4): 427 209-220. 428
45. 45. Pathogenic mechanisms of periodontitis-associated pregnancy complications. *Ann Periodontol*, 1998; 3(1): 233-250.
46. Yeo A, Smith MA, Lin D. et al. *Campylobacter rectus* mediates growth restriction in pregnant mice. *J Periodontol*, 2005; 76(4): 551-557.
47. Lin D, Smith MA, Champagne C, Elter J, Beck J, Offenbacher S. *Porphyromonas* 433 *gingivalis* infection during pregnancy increases maternal tumor necrosis factor alpha, 434 suppresses maternal interleukin-10, and enhances fetal growth restriction and 435 resorption in mice. *Infect Immun*, 2003; 71(9): 5156-5162. 436
48. .Dasanayake AP, Li Y, Wiener H, Ruby JD, Lee MJ. Salivary *Actinomyces naeslundii* 436 genospecies 2 and *Lactobacillus casei* levels predict pregnancy outcomes. *J Periodontol*, 2005; 76(2): 171-177.
49. McCormick MC. The contribution of low birth weight to infant mortality and childhood morbidity. *N Engl J Med.*, 1985; 312(2): 82-90
50. Weidlich P, Cimoës R, Pannuti CM, Oppermann RV. Association between periodontal diseases and systemic diseases. *Braz Oral Res* 2008;22:32-43.
51. Scannapieco FA, Bush RB, Paju S. Association between periodontal disease and risk for nosocomial bacterial pneumonia and chronic obstructive pulmonary disease: A systematic review. *Ann Periodontol* 2003;8:54-69.