International Journal of Research and Review
www.ijrrjournal.com E-ISSN: 2349-9788; P-ISSN: 2454-2237

Review Article

Relationship between Periodontitis and Systemic Diseases: A Review

Dr. Kamal Kishor Mankar[1], Dr. Sushil Naik[2], Dr. Swapnil Patil[3]

[1]Associate Professor, Department of Periodontics and Implantology, VSPM Dental College and research centre, Nagpur.
[2]Lecturer, Department of Public Health Dentistry, VSPM Dental College and Research Centre, Nagpur.
[3]Lecturer, Department of Conservative Dentistry and endodontics, VSPM Dental College and Research Centre, Nagpur.

Corresponding Author: Dr. Kamal Kishor Mankar

ABSTRACT

The potential impact on the periodontium of many systemic diseases have been well documented, much less is known about the consequences of diseased periodontium on systemic status. Periodontal medicine is a rapidly emerging branch of periodontology, based on abundance of evidence establishing a strong relationship between periodontal health or disease and systemic health or disease. Research has established that periodontal infection is a probable risk factor for cardiovascular disease, including atherosclerosis, myocardial infarction and stroke. Many studies also suggest that periodontitis may also contribute to adverse pregnancy outcomes, diabetes, respiratory diseases and other conditions. The anatomic closeness of this micro-flora to the blood stream can facilitate bacteremia and systemic spread of bacterial products, components and immune complexes. The findings from cross-sectional and longitudinal epidemiological studies are supported by in vitro and animal studies describing the plausible mechanism linking periodontal infection to development of atherosclerotic diseases, to the triggering of clinical coronary events or to both. It is possible that periodontal infection may serve as initiator or propagators of insulin resistance in a way similar to obesity, thereby aggravating glycemic control. Based upon the criteria that have been used to establish risk, data from animal and human studies support the biological plausibility that untreated moderate to severe periodontitis may increase the risk for adverse pregnancy outcome.

Keywords: Periodontitis, atherosclerosis, diabetes mellitus, inflammation,

INTRODUCTION

William Hunter a British physician in 1900 put forth the concept of "oral sepsis as a cause of wide range of systemic diseases" [1] Frank billings in 1911 replaced the term oral sepsis with focal infection, and advocated removal of all foci of infection. [2] The theory of focal infection stated that foci of sepsis were responsible for initiation and progression of variety of inflammatory diseases such as arthritis, peptic ulcers, and appendicitis. [3] Therapeutic edentulation was common as a result of the popularity of the focal infection theory. Since many teeth were extracted without evidence of infection thereby providing no relief of symptoms the theory was discredited and ignored for many years. The potential impact on the periodontium of many systemic diseases have been well documented, much less is known about the consequences of diseased periodontium on systemic status. Periodontal medicine is a rapidly emerging branch of periodontology, based on abundance of evidence establishing a strong relationship between periodontal health or

disease and systemic health or disease. The term periodontal medicine was first suggested by Offenbacher. [4] Recent research has established that periodontal infection is a probable risk factor for cardiovascular disease, including atherosclerosis, myocardial infarction and stroke. Many studies also suggest that periodontitis may also contribute to adverse pregnancy outcomes, diabetes, respiratory diseases and other conditions. [5] Recent progress in classification and identification of oral micro-organism and that certain micro-organism are normally found only in the oral cavity have opened the way for a more realistic assessment of importance of oral focal infection. Oral cavity can act as site of origin for dissemination of the pathogenic organism to distant body sites especially immunocompromised hosts. Human periodontal infections are associated with complex microfloras in which approximately 200 species (in apical periodontitis' [6] and more than 500 species (in marginal periodontitis) have been encountered. [7] The anatomic closeness of this micro-flora to the blood stream can facilitate bacteremia and systemic spread of bacterial products, components and immune complexes. Three mechanisms have been proposed to link oral infection with systemic diseases. [8]

Metastatic infection:

Oral infection and dental procedures can cause transient bacteremia. The microorganisms that gain entrance to the blood and circulate throughout the body are usually eliminated by the reticuloendothelium system within minutes (transient bacteremia). However if the disseminated microorganisms find favorable conditions, they may settle at a given site, and after a certain time lag start to multiple.

Metastatic injury.

Some microorganisms have the ability to produce diffusible proteins, or exotoxins, which include cytolytic enzymes and dimeric toxins with A and B subunits. The exotoxins are considered the most powerful and lethal poisons known. [9] conversely; endotoxins are part of the outer membranes released after cell death. Endotoxins is compositionally a lipopolysaccharide (LPS) that when introduced into the host, give rise to a variety of pathological manifestations. LPS is continuously shed from periodontal gram-negative rods during their growth in vivo. [10]

Metastatic inflammation.

Soluble antigens may enter the bloodstream, react with circulating specific antibody, and form a macromolecular complex. These immunocomplexes may give rise to variety of acute and chronic inflammatory reactions at the sites of deposition. [11]

Periodontitis and systemic disease susceptibility:

Roy C. Page proposed that periodontitis may affect the host's susceptibility to systemic disease in three ways. [12]

Shared risk factors

Factors that place the individual at high risk for periodontitis may also place them at high risk for systemic diseases such as cardiovascular disease. Among the environmental risk factors and indicators shared by periodontitis, and systemic diseases such as cardiovascular disease, are tobacco smoking, stress, aging, race or ethnicity, and male gender. It seems likely that the polymorphisms in the IL-1β and TNF-α gene, families are likely to associated with cardiovascular disease as well as with periodontitis.

Subgingival biofilms

Subgingival biofilms constitute an enormous and continuing bacterial load. They present continually renewing reservoirs of LPS and other gram-negative bacteria with ready access to the periodontal tissues and circulation. Systemic challenge with gram-negative bacteria or LPS induces vascular responses, including an inflammatory cell infiltrate in the vessel wall, vascular smooth muscle proliferation, vascular fatty degeneration, and intravascular coagulation. [13,14] PS

upregulates expression of endothelial cell adhesion molecules and secretion of interleukin-1 (IL-1), tumor necrosis factor alpha (TNF-α), and thromboxane, which results in platelet aggregation and adhesion, formation of lipid-laden foam cells, and cholesterol and cholesterol esters.

Periodontium as cytokine reservoir

The proinflammatory cytokines TNF-α, IL-1β, and gamma interferon as well as prostaglandin E2 (PGE2) reaches high tissue concentrations in periodontitis. The periodontium can serve as a renewing reservoir for spillover of these mediators, which can enter the circulation and induce and perpetuate systemic effects. IL-1β favors coagulation and thrombosis and retards fibrinolysis. [15] IL-1, TNF-α, and thromboxane can cause platelet aggregation and adhesion, formation of lipid-laden foam cells and deposition of cholesterol. These mediators from the diseased periodontium may also account for preterm labour and low-birth weight infants.

Cardiovascular diseases: Cardiovascular diseases (CVD) such as atherosclerosis & myocardial infarction occur as a result of complex set of genetic and environmental factors. [16] Genetic factors include age, lipid metabolism, obesity, hypertension, diabetes, increased fibrinogen levels. Environmental factors include socio-economic status, exercise stress, non steroidal anti inflammatory drugs, smoking and chronic infection. The classical risk factors of Cardiovascular diseases such as hypertension, hypercholesterolemia and cigarette smoking can only account for one half to two third of variation in the incidence of CVD. Among other possible risk factors evidence linking chronic infection and inflammation to CVD has been accumulating. [17,18] It is clear that periodontal disease is capable of predisposing individual to CVD, given the abundance of gram negative species involved, the readily detectable levels of proinflammatory cytokines, the heavy immune and inflammatory infiltrate involved, the association of high peripheral fibrinogen and WBC count. [19]

Mechanisms:

There are several mechanism proposed by which periodontal disease may trigger pathways leading to cardiovascular disease through direct and indirect effects of oral bacteria. Evidence indicates that oral bacteria such as *Streptococcus sanguis* and *Porphyromonas gingivalis* induce platelet aggregation which leads to thrombus formation. [20] These organisms have a collagen like molecule, the platelet aggregation associated protein on their surface. [21] The second factor in this process could be an exaggerated host response to a given microbial or LPS challenge as reflected in the release of high levels of proinflammatory mediators such as PGE2, TNF-α, IL-1β. [22] These mediators have been related to interindividual differences in the T-cell repertoire and the secretary capacity of monocytic cells. Peripheral monocytes from individuals with the hyperinflammatory monocyte phenotype secrete 3 to 10 fold greater amounts of these mediators in response to LPS than those from normal monocyte phenotype individuals. [23] Patient with certain forms of periodontal disease, such as aggressive periodontitis, refractory periodontitis possess a hyperinflammatory monocyte phenotype. [24] A third mechanism possibly involves the relationship between bacterial and inflammatory products of periodontitis and CVD. LPS from periodontal organisms being transferred to the serum as a result of bacteremia or bacterial invasion may have a direct effect on endothelium so that atherosclerosis is promoted. [25] LPS may also elicit recruitment of inflammatory cells into major blood vessels and stimulates proliferation of vascular smooth muscle, vascular fatty degeneration, intravascular coagulation and blood platelet function. These changes are the result of the action of various biological mediators, such as PGE2, TNF-α, IL-1β on vascular endothelium and smooth muscle. [26] Fibrinogen and WBC count increases noted in periodontitis

patient may be a secondary effect of the above mechanisms or a constitutive feature of those at risk for both CVD and periodontitis. [27] Periodontitis as an infection may stimulate the liver to produce C- reactive protein (CRP) a marker of inflammation, which in turn forms deposits on injured blood vessels. CRP binds to cells that are damaged and fixes complement, which activates phagocytes, including neutrophils. These cells release nitric oxide, there by contributing atheroma formation. In a study of 1043 apparently healthy men, baseline plasma concentrations of CRP predicted the risk of future myocardial infarction and stroke. Ebersole et al. found that patient with adult periodontitis have higher levels of CRP and haptoglobin than subjects without periodontitis. A specific heat shock protein Hsp65 has been reported to link cardiovascular risks and host response. [28] It has been suggested that chronic oral infection stimulates high levels of Hsp65 in subjects with high cardiovascular risk. [29] Thus, if antibodies directed towards bacterial shock proteins cross-react with heat shock proteins expressed in the host tissue, especially if they are found in the lining of blood vessels, then some oral species might well be the link between oral infection and cardiovascular disease.

Diabetes mellitus: Diabetes mellitus is a clinical syndrome characterized by hyperglycemia due to an absolute or relative deficiency of insulin. Diabetes mellitus is characterized by metabolic abnormalities and long-term complications involving the eyes, kidneys, nervous system, vasculature and periodontium. [30] Diabetes is commonly categorized as type 1, or insulin dependent diabetes, and type-2, non- insulin dependent. The fundamental derangement in insulin dependent diabetes is the hypoproduction of insulin due to destruction of beta cells of the pancreas. In non-insulin-dependent diabetes, the derangement involves resistance of the target tissue to insulin action. Although the precise etiology is still uncertain in both main types of primary diabetes, environmental factors interact with a genetic susceptibility to determine which of those with the genetic predisposition actually develops the clinical syndrome and the timing of its onset. Environmental factors in insulin- dependent diabetes include virus, diet, immunological factors and pancreatic diseases. In non-insulin- dependent diabetes, environmental factors include life style, age, pregnancy, pancreatic pathology, and insulin secretion and resistance. Severe periodontal disease often coexists with severe diabetes mellitus. Diabetes is a risk factor for severe periodontal disease. The converse possibility that periodontal disease either predisposes or exacerbates the diabetic condition has received more and more attention.

Mechanism

A model was presented by Grossi and Genco, in which severe periodontal disease increases the severity of diabetes mellitus and complicates metabolic control. [31] They propose that an infection-mediated upregulation cycle of cytokine synthesis and secretion by chronic stimulus from LPS and products of periodontopathic organisms may amplify the magnitude of the advanced glycation end products (AGE) mediated cytokine response that is operative in diabetes mellitus. The combination of these two pathways, infection and AGE mediated cytokine upregulation, helps explain the increase in tissue destruction seen in diabetic periodontitis, and how periodontal infection may complicate the severity of diabetes and the degree of metabolic control, resulting in a two-way relationship between diabetes and periodontal disease or infection. It is well established that diabetic are more likely to develop periodontal disease than nondiabetics [32] and the disease severity is related to the duration of diabetes. One plausible biologic mechanism for why diabetics have more severe periodontal disease is that glucose-mediated AGE accumulation affects the migration and phagocytic activity of the mononuclear and polymorphonuclear phagocytic cells,

resulting in establishment of a more pathogenic subgingival flora. The maturation and gradual transformation of the subgingival microflora into an essential gram-negative flora. This provides a chronic source of systemic challenge via the ulcerated pocket epithelium. This in turn triggers an "infection mediated" pathway of cytokine upregulation, especially with secretion of TNF-α & IL-1, and a state of insulin resistance, affecting glucose utilizing pathway. The interaction of mononuclear phagocytes with AGE- modified proteins induces upregulation of cytokine expression and induction of oxidative stress. Simultaneously periodontal infection may induce a chronic state of insulin resistance, contributing to the cycle of hyperglycemia, nonenzymatic irreversible glycation, and AGE- protein binding and accumulation, amplifying the classical pathway of diabetic connective tissue degradation, destruction, and proliferation. [31] Hence the relationship between diabetes mellitus and periodontal disease or infection becomes two ways. A self-feeding two-way system of catabolic response and tissue destruction ensues, resulting in more severe periodontal disease and increased difficulty in controlling blood sugar.

Epidemiological Evidence:

The results of a longitudinal study indicated that severe periodontitis at baseline is associated with increased risk of poor glycemic control at follow-up two or more years later. [33] These finding suggest that severe periodontitis may be an important risk factor in progression of diabetes, and control of periodontal infection is essential to achieve long term control of diabetes mellitus. Grossi and Genco reexamined the studies that addressed the effect of periodontal treatment on metabolic control of diabetes mellitus and concluded that the effect of periodontal on diabetic metabolic control is dependent on the mode of therapy. When mechanical periodontal treatment alone is provided, regardless of the severity of periodontal disease or degree of diabetes control, the treatment outcome is strict improvement in periodontal status or a local effect. On the contrary, when systemic antibiotics are included with mechanical therapy, an improvement in diabetes control, measured as a reduction in glycated hemoglobin or reduction in insulin requirement is achieved. Therefore one may propose that control of chronic gram-negative periodontal infection should be a part of standard treatment of the diabetic patient.

Adverse pregnancy outcome:

Recently the impact of periodontal disease on adverse pregnancy outcome has received much attention. Pre-term low birth weight (PLBW) is a problem encountered in most world communities at varying levels of prevalence. There is emerging interest and increasing amount of the evidence that support the inter-relationship between periodontitis and adverse pregnancy outcome. Growth in uterus is a balance between the genetic potential of each individual fetus and the maternal environment. The maintenance of a normal pregnancy for approximately nine months represents the balance of the maternal and fetal nutritional, hormonal, and immunological systems. The international definition of low birth weight adopted by the 29th World Health assembly in 1976 is a birth weight <2500 g. Birth weight <2500 g results in rapid increase in risk of infant mortality. Low birth weight can be a result of a short gestational period and/or retarted intrauterine growth. These low birth weight infants are more likely to die during the neonatal period, and low birth weight survivors are more likely to develop neuro-developmental problems, respiratory problems and congenital problems. The neonatal and long term health care cost of pre- term infants impose a considerable economic burden both on individual families and taxpayers. Many risk factors have been proposed for pre-term rupture of membrane and preterm labour, including infection and inflammation. [34] 25% to 50% of PLBW deliveries occur without any known etiology, and there is increasing

evidence that infection may play a significant role in pre- term delivery. Both generalized infections, including viral respiratory infections, diarrhea and malaria, and more localized infections of the genital and urinary systems can affect the gestational length. Association between chorioamnionitis, infection of amniotic fluid and PLBW has been established. [35] PLBW is multifactorial in nature. The traditional risk factors are smoking, genetics, and use of alcohol, prenatal care, poor maternal nutrition and urinary tract infection. About 25% of PLBW cases occur without a candidate or suspected risk factors. Gibbs in his review article provides an excellent outline of the possible association between infections and adverse pregnancy outcomes. The infection hypothesis suggest that during a subclinical infection, the micro-organisms and their lipopolysaccharides enter the uterine cavity during pregnancy by the ascending route from the lower genital tract or by the blood- borne route from a non-genital route, hence causing pre-term birth. [36] It has been suggested that spontaneous pre- term labour is commonly associated with bacterial vaginosis, a vaginal condition characterized by a prevalence of anaerobes. Bacterial invasion of the choriodecidual space can activate the fetal membranes or trigger the maternal immune system to produce a variety of cytokines and growth factors. This has been shown to be eliciting an inflammatory burden resulting in placental damage and distress and, hence fetal growth restriction. In addition the cascade of disordered cytokine response can lead to stimulation of prostaglandin synthesis and release of matrix metalloprotinases (MMPs), which account for the uterine contractions and membrane rupture, respectively leading to the induction of labour. [37]

Epidemiological Evidence: In the early 1990s Offenbacher et al. hypothesized that oral infection, such as periodontitis, could represent a significant source of both infection and inflammation during pregnancy, [38] they noted that periodontal disease is a gram-negative anaerobic infection, which may lead to bacteraemia and induce pregnancy complication. In a series of landmark animal studies, they demonstrated that in a hamster chamber model, chronic exposure to *Porphyromonas gingivalis* led to 15% to 18% decrease in fetal weights along with a local increase of PGE2 and TNF-α within the chamber fluid. Later they studied the association between infection and pregnancy by inducing periodontal disease in the hamster model. These animal studies provided vital proof-of-principle experiments and suggested the possibility that low-grade oral infections may trigger off maternal-fetal inflammation and result in adverse pregnancy events. In subsequent landmark human study, Offenbacher et al. show that periodontitis was a significant risk factor for PLBW. The adjusted odd ratios were 7.9 and 7.5 for all PLBW and primiparous PLBW cases respectively. Jeffcoat et al conducted a prospective cohort study of 1313 pregnant women with severe periodontitis. [39] There was an adjusted odd ratio of 4.45 for preterm delivery before 37 weeks' gestation age, 5.28 before 35 weeks and 7.07 for delivery before 32 weeks.

Summary:

The findings from cross-sectional and longitudinal epidemiological studies are supported by in vitro and animal studies describing the plausible mechanism linking periodontal infection to development of atherosclerotic diseases, to the triggering of clinical coronary events or to both. The cumulative evidence supports, but does not prove, a causal association between periodontal infection and atherosclerotic cardiovascular disease or its sequelae. Consequently, more focused studies are needed to elucidate the mechanism involved. Periodontal infection and diabetes mellitus are closely associated and are highly prevalent chronic diseases with many similarities in pathobiology. Related antecedent conditions including obesity and insulin resistance may play an important role in this relationship; inflammation is a

critical player in the relationship. Diabetes clearly increases the risk for periodontal diseases, and biologically plausible mechanisms have been demonstrated in abundance. It is possible that periodontal infection may serve as initiator or propagators of insulin resistance in a way similar to obesity, thereby aggravating glycemic control. Further research is needed to clarify this aspect of the relationship between periodontal infection and diabetes. Based upon the criteria that have been used to establish risk, data from animal and human studies support the biological plausibility that untreated moderate to severe periodontitis may increase the risk for adverse pregnancy outcome. Further, emerging intervention studies have reported that performing SRP in pregnant women with periodontitis may reduce the pre-term births in this population. In this era of evidence-based medicine further work needs to be done to establish the association. Larger sample populations and randomized intervention studies are required to substantiate the effects of periodontal therapy in reducing the risk of adverse pregnancy outcome. Presently, the major rationale for the treatment of periodontal disease is to prevent progression of the disease to preserve the dentition. Evidence suggests that periodontal infection is a potential contributing factor to a rather wide variety of systemic diseases. In the future, an additional rationale for periodontal therapy may be to prevent untoward effects on systemic health. Further intervention studies are needed to clarify the impact of the treatment of periodontal infections to manage or prevent systemic conditions. Indeed, as a healthcare professionals working as a team, an understanding of periodontal-systemic relationship and its implications will further enhance the quality of medical and dental care being provided to patients.

REFERENCES

1. Hunter W. Oral sepsis as a cause of disease. *Br Med J* 1900:1: 215–216.
2. Billings F. Chronic focal infections and their etiologic relations to arthritis and nephritis. *Arch Intern Med* 1912: 9:484–498.
3. Scannapieco, F. A. 1998. Position paper: periodontal disease as a potential risk factor for systemic diseases. *J. Periodontol.* 69:841-850
4. Offenbacher S. Periodontal diseases. Pathogenesis. *Ann Periodontol* 1996: 1: 821–878.
5. Soskolne WA. Epidemiological and clinical aspects of periodontal diseases in diabetics. *Ann Periodontol* 1998: 3:3–12.
6. Tronstad, L. 1992. Recent development in endodontic research. *Scan. J. Dent. Res.*100:52-59
7. Moore, W. E. C., and L. V. H. Moore. 1994. The bacteria of periodontal disease. *Periodontol. 2000* 5:66-77
8. Thoden van Velzen, S. K., L. Abraham-Inpijn, and W. R. Moorer. 1984. Plaque and systemic disease: a reappraisal of the focal infection concept. *J. Clin.Periodontol.*11:209-220.
9. Hammond, B. F. 1992. Major bacteri bacterial diseases, p. 165-190. *In* J. Slots, and M. A. Taubman (ed.), Contemporary oral microbiology and immunology. Mosby, St. Louis, Mo
10. McGhee, J. R. 1982. Microbial pathogenic mechanisms, p. 374-387. *In* J. R. McGhee, S. M. Michalek, and G. H. Cassell (ed.), Dental microbiology. Harper & Row, Philadelphia, Pa.
11. Van Dyke, T. E., V. R. Dowell, Jr., S. Offenbacher, W. Snyder, and T. Hersh. 1986. Potential role of microorganisms isolated from periodontal lesions in the pathogenesis of inflammatory bowel disease. *Infect. Immun.* 53:671- 677.
12. Page, R. C. 1998. The pathobiology of periodontal diseases may affect systemic diseases: inversion of a paradigm. *Ann. Periodontol.* 3:108-120.
13. Marcus, A. J., and D. P. Hajjar. 1993. Vascular transcellular signaling. *J.Lipid Res.* 34:2017-2031.
14. Mattila, K. J. 1989. Viral and bacterial infections in patients with acute myocardial infarction. *J. Intern. Med.* 225:293-296.
15. Clinton, S. K., J. C. Fleet, H. Loppnow, R. N. Salomon, B. D. Clark, J. G. Cannon, A. R. Shaw, C. A. Dinarello, and P. Libby. 1991. Interleukin-1 gene expression in rabbit vascular tissuein vivo. *Am. J. Pathol*. 138:1005-1014.
16. Herzberg, M. C., and M. W. Weyer. 1998. Dental plaque, platelets, and cardiovascular diseases. *Ann. Periodontol*. 3:151-160.
17. Syrjänen, J. 1990. Vascular diseases and oral infections. *J. Clin. Periodontol.* 17:497-500
18. Valtonen, V. V. 1991. Infection as a risk factor for infarction and atherosclerosis. Ann. Med. 23:539-543.

19. Kinane, D. F. 1998. Periodontal diseases' contributions to cardiovascular disease: an overview of potential mechanisms. Ann. Periodontol. 3:142-150.
20. Herzberg, M. C., and M. W. Meyer. 1996. Effects of oral flora on platelets: possible consequences in cardiovascular disease. J. Periodontol. 67:1138-1142.
21. Herzberg, M. C., G. D. MacFarlane, P. Liu, and P. R. Erickson. 1994. The platelet as an inflammatory cell in periodontal disease: interactions with *Porphyromonas gingivalis*, p. 247-255. *In* R. Genco, S. Hamada, T. Lehner, J. McGhee, and S. Mergenhagen (ed.), Molecular pathogenesis of periodontal disease. American Society for Microbiology, Washington, D.C.
22. Hernichel-Gorbach, E., K. S. Kornman, S. C. Holt, F. Nichols, H. Meador, J.T. Kung, and C. A. Thomas. 1994. Host responses in patients withgeneralized refractory periodontitis. *JPeriodonto*l. 65:8-16.
23. Offenbacher, S., J. G. Collins, B. Yalta, and G. Haradon. 1994. Role of prostaglandins in high-risk periodontitis patients, p. 203-214. *In*R. Genco, S. Hamada, T. Lehner, J. McGhee, and S. Mergenhagen (ed.), Molecular pathogenesis of periodontal disease. American Society for Microbiology, Washington, D.C.
24. Shapira, L., W. A. Soskolne, M. N. Sela, S. Offenbacher, and V. Barak. 1994. The secretion of PGE2, IL-1 beta, IL-6, and TNF alpha by adherent mononuclear cells from early onset periodontitis patients. *J. Periodontol.* 65:139-146.
25. Pesonen, E., E. Kaprio, J. Rapola, T. Soveri, and H. Oksanen. 1981. Endothelial cell damage in piglet coronary artery after intravenous administration of *E. coli* endotoxin: a scanning and transmission electron-microscopic study. *Atherosclerosis* 40:65-73.
26. Beck, J. D., R. I. Garcia, G. Heiss, P. S. Vokonas, and S. Offenbacher. 1996. Periodontal disease and cardiovascular disease. J. Periodontol. 67:1123-1137.
27. Kweider, M., G. D. Lowe, G. D. Murray, D. F. Kinane, and D. A. McGowan. 1993. Dental disease, fibrinogen and white cell count: links with myocardial infarction? *Scott. Med. J.* 38:73-74.
28. Xu, Q., G. Luef, S. Weimann, R. S. Gupta, H. Wolf, and G. Wick. 1993. Staining of endothelial cells and macrophages in atherosclerotic lesions with human heat-shock protein-reactive antisera. Arterioscler. Thromb. 13:1763-1769.
29. Loesche, W. J., and D. E. Lopatin. 1998. Interactions between periodontal disease, medical diseases and immunity in the older individual. *Periodontol. 2000* 16:80- 105.
30. Foster, D. W. 1994. Diabetes mellitus, p. 1979-2000. *In* K. J. Isselbacher, E. Braunwald, J. D. Wilson, J. B. Martin, A. S. Fauci, and D. L. Kasper (ed.), Harrison's principles of internal medicine. McGraw-Hill, New York, N.Y.
31. Grossi, S. G., and R. J. Genco. 1998. Periodontal disease and diabetes mellitus: a two-way relationship. Ann. Periodontol. 3:51-61
32. Papapanou, P. N. 1996. Periodontal diseases: epidemiology. *Ann. Periodontol*. 1:1-36
33. Shlossman, M., W. C. Knowler, D. J. Pettitt, and R. J. Genco. Type 2 diabetes mellitus and periodontal disease. *J. Am. Dent. Assoc*. 121: 532-536
34. Kramer MS. Determinants of low birth weight: methodological assessment and meta-analysis. Bull World Health Organ 1987;65:663-737.
35. Offenbacher S, Odle BM, Van Dyke TE. The use of prostaglandin E2 as a predictor of periodontal attachment loss. *J Periodont Res* 1986; 21:107-12.
36. Gibbs RS. The relationship between infection and adverse pregnancy outcomes: an overview. *Ann Periodontol* 2001;6:153-63.
37. Romero R, Mazor M, Sepulveda W, Avila C, Copeland D, Williams J. Tumor necrosis factor in preterm and term labor. *Am J Obstet Gynecol*1992;166;1576-87.
38. Collins JG, Smith MA, Arnold RR, Offenbacher S. Effects of *Escherichia coli* and *Porphyromonas gingivalis* lipopolysaccharide on pregnancy outcome in the golden hamster. *Infect Immun* 1994;62:4652-5.
39. Jeffcoat MK, Geurs N, Reddy MS, Cliver SP, Goldenberg RL, Hauth JC. Periodontal infections and preterm birth: results of a prospective study. *J Am Dent Assoc* 2001; 132:875-80.

How to cite this article: Mankar KK, Naik S, Patil S. Relationship between periodontitis and systemic diseases: a review. 2018; 5(11):172-179.

******