Silent Link between periodontitis and systemic diseases: A Brief Review

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Recent research has fielded conflicting data regarding the relationship between dental disease, and systemic effect such as diabetes, pneumonia, cardiovascular disease, preterm delivery of low birth-weight infants and preeclampsia. A causative relationship would have major ramifications for health care. There is a plausible theoretical basis for such a link, as increased levels of inflammatory mediators may increase the risk of atherosclerotic plaque formation. Postulated mechanisms include translocation of periodontal pathogens to the fetoplacental unit and action of a periodontal reservoir of lipopolysaccharides or inflammatory mediators. Hence, periodontal treatments and oral hygiene instructions are essential to prevent future complications among those with periodontitis.

Key words: Periodontitis, pre-eclampsia, cardiovascular disease, Diabetes, Pneumonia, low birth weight.

Introduction

The theory of focal infection, which was promulgated during 19th and early 20th centuries, stated that "face" of sepsis were responsible for the initiation and progression of a variety of inflammatory diseases such as arthritis, peptic ulcers, and appendicitis[1]. Before the development of modern periodontal treatment, many teeth were extracted prophylactically because of the focal infection theory.[2,3] Recent progress in classification and identification of oral micro-organisms and the realization that certain micro-organisms are normally found only in the oral cavity have opened the way for a more realistic assessment of the importance of oral focal infection. It has become increasingly clear that the oral cavity can act as the site of origin for dissemination of pathogenic organisms to distant body sites, especially in immunocompromised hosts such as patients suffering from malignancies, diabetes, or rheumatoid arthritis or having corticosteroid or other immunosuppressive treatment. A number of epidemiological studies have suggested that oral infection, especially marginal and apical periodontitis may be a risk factor for systemic diseases[4-7]. It has been also be reported that periodontal disease may be a separate risk factor for cardiovascular disease, cerebrovascular disease and respiratory disease, preterm delivery of low-birth weight infants as well as pre-eclampsia[8-9].

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Pathways linking oral infection to secondary non-oral disease

It has been proposed that three pathways linking oral infections to secondary systemic effects[10]:

Metastatic infection

Metastatic injury

Metastatic inflammation

Periodontal disease affects susceptibility to systemic disease

Periodontal disease is defined as multifunctional disease that cause inflammation and destruction of the attachment apparatus of the teeth. Periodontal disease is caused by bacteria found in dental plaque, and about more than ten species have been identified as putative pathogens in periodontal disease, mainly gramnegative rods. Actinobacillus actinomycetemcomitans, porphyromonas gingivales, and bacteriods forsythus are the gram-negative bacteria most commonly

associated with periodontitis[11-12]. Periodontitis may affect the host's susceptibility to systemic disease in three ways: by shared risk factors, by subgingival biofilms acting as reservoirs of gram-negative bacteria, and through the periodontium acting as a reservoir of inflammatory mediators.[13]

Shared risk factors by periodontitis and cardiovascular disease[13]. Number of risk factor such as tobacco smoking, stress, aging, race or ethnicity, and male gender shared by both diseases.

Shared risks factors by periodontitis and preterm delivery of low birth weight Infants : (PLBW) :

Identified shared risk factors for PLBW and periodontitis include older (>34 years) and younger (< 17 years) maternal age; African-American ancestry; low socioeconomic status; in adequate prenatal care; drug, alcohol and tobacco abuse; hypertension; genitourinary tract infection; diabetes mellitus; and multiple pregnancies. Smoking during pregnancy has been linked to 20% - 30% of PLBW and 10% of fetal and infant deaths[14].

Subgingival biofilms : Subgingival biofilms containing heavy bacterial load. The bacterial load against an ulcerated sulcular epithelium can exceed 109-1010 total bacteria in a patient with periodontal disease. The periodontium is a highly vascular tissue and when inflamed, the gingival capillary endothelial cells proliferate to form a dense nexus of granulomatous material that lie immediately subadjacent to the periodontal pocket. As a consequence of persistent inflammatory cell activation, the level of pro-inflammatory mediator within the periodontal tissue is extraordinarily high.[15] Periodontal disease may serve as a potential reservoir for inflammatory cytokines to reach the systemic circulation. Consistent with this concept, subjects with periodontitis have been reported to have elevations of serum IL-I?, TNF-?, IL-6 and C-reative protein[16-17]. Hence periodontitis can represent an inflammatory stress or by the release of potentially deleterious mediators of inflammation into circulation.

Periodontal reservoir of LPS and inflammatory mediators: It has been suggested that the possibility of indirect action of translocated bacterial products such as endotoxins (such as LPS)[18]. LPS stimulate production of prostaglandins by the placenta and chorioamnion, and elevated concentrations of LPS have been measured in the amniotic fluid in cases of PLBW19. Pro-inflammatory cytokines IL-I, IL-6 and TNF-? can cross human fetal membranes, and it is plausible that the high concentrations of these cytokines that are generated at sites of chronic periodontitis and measured at higher levels in the plasma of patients with periodontitis could influence the fetoplacental unit and contribute to PLBW[13,20].

Pre-eclampsia and periodontitis

Pre-eclampsia is a dangerous disease of human pregnancy, which affects both the mother and her fetus[21]. There are two syndromes in preeclampsia. The first is maternal, characterized by endothelial cell activation, hypertension and proteinuria. The second is fetal, manifested primarily by intrauterine growth restriction. The symptoms of this syndrome appear during the second and third trimester of pregnancy [22-23]. Pre-eclampsia should probably be regarded as a syndrome of heterogeneous origin [24]. Different factors have been postulated to be contributory, genetic, immune, obesity, hormone and race[21,25]. The known risk factors for pre-eclampsia include primiparity, nulligravidity, obesity, renal disease, uterine malformation, fetal hydrops, elevated serum lipid ratio, non-smoking, no prenatal care and diabetes[24,26]. It has been reported that maternal periodontal disease during pregnancy is associated with an increased risk for the development of pre-eclampsia9. It has been suggested that the mechanisms described in the development of atherosclorosis resemble the pathophysiological mechanisms described in pre-eclampsia, and are associated with infectious agents [22,23].

Cardiovascular disease and periodontitis

Recent research has yield conflicting data regarding the relationship between dental disease, particularly periodontitis, and cardiovascular disease. Epidemiological associations between periodontitis and cardiovascular disease have been reported[26-32]. It has been reported that periodontal disease, through its mostly gram-negative pathogens,

provides a biological burden of endotoxin and inflammatory cytokines, which may initiate and exacerbate atherogenesis or thromboembolic events[33]. Some workers showed that P.gingivalis can actively adhere to and invade fetal bovine heart endothelial cells, bovine aortic endothelial cells, and human umbilical vein endothelial cells. Invasion efficiencies of 0.1, 0.2, and 0.3% were obtained with bovine aortic endothelial cells, human umbilical vein endothelial cells, and fetal bovine heart endothelial cells respectively. A specific heat shock protein, HSP65, has been reported to link cardiovascular risks and host responses[35]. Heat shock proteins are important for the maintenance of normal cellular function and may have additional roles of virulence factors for many bacterial species[36]. The interaction between expressed HSP65 and the immune response induced by bacterial infection is hypothesized to be responsible for the initiation of the early atherosclerotic lesion.[37]

It has been suggested that chronic oral infection stimulates high levels of HSP65 in subjects with high cardiovascular risk[38]. There is a plausible theoretical basis for such a link, as increased levels of inflammatory mediators may increase the risk of atherosclerotic plaque formation. Nevertheless, a clinical conformation of a causative relationship has been difficult, in part because cardiovascular disease and periodontal disease share common risk factors such as increasing age and tobacco use, and because cardiovascular medications may increase the risk of periodontitis. Patients should be encouraged to control documented risk factors for cardiovascular disease and to maintain oral health for its well known health benefits[39].

Preterm birth, growth restriction and periodontitis

It has been evident that a significant association between periodontal disease and pregnancy complications including premature delivery (gestational age <37 weeks, decreased fetal weight (birth weight (BW) <2500 g) [40]. Pregnancy outcomes were evaluated in these animals after either the establishment of experimental periodontitis, the establishment of a non-disseminating subcutaneous tissue infection with porphyromonas gingivalis or intravenous infection of LPS from P. gingivalis. Fetal weights were significantly lower in the experimental animals, and the severity of the fetal effects was directly related to the levels of PGE2 and TNF-?[41-43]. The role of periodontal infection as a possible risk factor for PLBW more likely in valves translocation of bacterial products LPS or inflammatory medicitors (specificially IL-6, TNF-? and PGE2) rather than bacteremic spread and translocation of the bacteria themselves[44]. Most bacteria associated with progressive periodontitis are anaerobes which in aerobic settings they would rarely survive to enter the blood stream letalone establish an infection in the fetoplacental unit. It has been proposed that in the absence of red complex organisms, or the presence of a protective maternal antibody response to both organ and red complex organisms, there would not be a significant increase in the rate of fetal exposure or pregnancy complication. However, in the absence of a protective maternal antibody response, fetal exposure and preterm complications are likely to occur[45].

Periodontitis and Pneumonia

Community -acquired pneumonia often is caused by organisms considered to be common residents of the upper airways, including the following: Streptococcus pneumonia, Heamophilus influenzae, Mycoplasma pneumoniae, Chlamydia pneumoniae,Legionella pneumophila,Candida albicans and anaerobic bacteria (often those associated with periodontal disease). Nosocomial pneumonia often is caused by gram-negative enteric bacteria such as E.coli,Klebsiella pneumoniae and other enteric species ;Pseudomonas aeruginosa; and Staphylococcus aureus.A related disease is aspiration pneumonia ,which is caused by anerobic organisms ,in turn typically derived from gingival cervice [46].Aspiration pneumonia often develops in patients at risk of aspirating oral contents into the lung ,such as those with dysphagia or depressed consciousness .Aspiration pneumonia occurs both in community and in institutional settings.

Periodontal disease and diabetes

A large evidence base suggested that diabetes is associated with an increased prevalence, extent

and severity of gingivitis and periodontitis .Furthermore, numerous mechanisms have been elucidated to explain the impact of diabetes on the periodontium .While inflammation plays an obvious role in periodontal diseases, evidence in medical literature also supports the role of inflammation as major component in the pathogenesis of diabetes and diabetic complications. Research suggests that, as in infectious process with a prominent inflammatory component, periodontal disease can adversely affect the metabolic control of diabetes. Conversely, treatment of periodontal disease and reduction of oral inflammation may have a positive effect on diabetic condition,although evidence for this remains somewhat equivocal[47].

Conclusion

Periodontal disease appears to be a new potential risk factor for pregnancy complications. Hence, periodontal treatments and oral hygiene instructions are essential to prevent future complications among pregnancy women particularly those with periodontitis. Pre pregnancy care and prenatal follow up for dental status is the most reasonable choice.

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