IJIRR

International Journal of Information Research and Review
Vol. 04, Issue, 11, pp.4712-4715, November, 2017

RESEARCH ARTICLE

PERIODONTITIS AND SYSTEMIC DISEASE- AN ELEMENTAL CATASTROPHE

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ARTICLE INFO

Article History:

Received 19th August, 2017
Received in revised form
09th September, 2017
Accepted 16th October, 2017
Published online 30th November, 2017

Keywords:

Periodontal disease,
Systemic diseases,
Diabetes, Cardiovascular diseases,
Pregnancy.

ABSTRACT

For decades physicians and dentists are paying their concentrations in their own respective fields specializing in medical sciences pertaining to the body and oral cavity respectively. Oral health may be an indicator of systemic health. Many studies have discussed about the relationship between periodontal disease and systemic disease and because of this relationship the allopathic medicine and the dental medicine is quickly closing. Among the systemic diseases cardiovascular disease, diabetes mellitus, pregnancy outcomes, osteoporosis, Alzheimer's disease and pre-term delivery have been associated with periodontal diseases. Researchers must continue to scratch more information regarding the correlations between the periodontal disease and systemic conditions. This review is an attempt to bring all the possible relations between periodontal diseases and systemic conditions.

INTRODUCTION

Pathobiology of Periodontal Diseases

Periodontal disease refers to an inflammatory condition that occurs in the tissues surrounding the tooth due to the bacterial invasion and chronic gingival inflammation. Result is the alveolar bone loss and the attachment loss from the tooth surface which ultimately results in tooth loss. Periodontal disease have many different stages starting from easily treatable to irreversible severe periodontitis. Periodontal disease is accentuated by a variety of risk factors like cigarette smoking, systemic diseases, medications such as steroids, anti-epileptic drug, cancer therapy drug, ill-fitting bridges, crooked teeth and loose fillings, pregnancy and oral contraceptive use (Loesche, 2001). Initiation of the periodontal disease starts with supra-gingival plaque accumulation followed by sub-gingival plaque formation. In the passage of time the bacteria presents in the plaque creates a dysbiosis which triggers the host defense cells to initiate some molecule which degrade our own connective tissue leading to the so called attachment loss in the periodontium. Anaerobic gram negetive bacteria are mainly responsible for the periodontal breakdown. Proinflammatory cells begin to accumulate in the region and secrete proinflammatory molecules which can directly cause the tissue damage.

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For the past 10 years many studies had been published indicating a positive or negative relationship between periodontal disease and various systemic disorders.

Periodontitis and Cardiovascular Disease

Cardiovascular disease is a common cause of death and it accounts for 29 % of the deaths worldwide (Amar, 2003). There are several other forms of CVD like high blood pressure, coronary heart disease, peripheral arterial disease and stroke with atherosclerosis. Atherosclerosis is responsible for 50% of the CVD mortality n USA, Japan and Europe (Lusis, 2000). Studies had shown that severe periodontal disease is associated with a 25% to 90% increase in CVD (Beck, 1996). One study shows that 91% of CVD patients portrayed moderate to severe periodontitis while 66% of the healthy patients had periodontitisand the cause for such correlation lies behind the mutual risk factors between atherogenesis and periodontal disease[5]. To consider periodontal disease as a potential risk factor for atherosclerosis and other CVD pathogens should be locally present in the atherosclerotic plaque which are highly associated with periodontitis. Investigating this concept Cairo et al detected T. forsythensisDNA in 79%, F. nucleatum DNA in 63%, P. intermedia in 53%, P.gingivalis in 37% and A. actinomycetemcomitans in 5% of the carotid atheroma patients (Cairo, 2004) samples.

Etiologically the chronic disease of periodontal microbes can lead to atherosclerosis via two pathways:

- The direct invasion of the arterial wall (Haraszthy, 2000).
- The release of systemic inflammatory mediators with atherogenic effects (Loos, 2000).

It was shown in various studies that the pathogen P. gingivalis shows the ability to interact with the endothelial surface and to induce smooth cell proliferation, causing damages and impairing the vasomotor functionality of the endothelial cells (Khlgatian, 2002). A very important biomarker to denote the link between periodontal disease and CVD is serum C reactive protein and it's level of elevation in the blood determines the endothelial dysfunctions. In patients with periodontitis whose plasma levels are elevated with fibrinogen (Thompson, Thompson, 1995) and TNF-α there is association with increased carotid intima-media thickness. Recent studies have shown that CRP may interfere with availability of endothelial nitric oxide (NO), by decreasing the expression of NO synthase and simultaneously increasing the production of reactive oxygen, which inactivates NO (Thompson, 2003). Elevated CRP levels in the serum are the signal feature of the transition of coronary artery disease to the formation of platelet rich thrombus following erosion. Another mechanism by which the bioavailability of NO is decreased is by oxidative inactivation by reactive oxygen species. LPS from the bacterial cell wall of P. gingivalis triggers the macrophages and other cells to release cytokines leading to systemic activation of phagocytic cells. PGE_2, TNF-α and IL -1 all reach high and potent systemic levels. These activated macrophages can then transform into foam cells, inducing the production of pro-inflammatory cytokines, leading to endothelial dysfunction (Chun, 2005). In a recent study by Pussinen et al found out that periodontitis diminished the antiatherogenic potency of high density lipoprotein further increasing the risk of CVD (Pussinen, 2004). New findings have suggested that tooth loss, rather than periodontal disease may be an important link between CVD and oral health. Elter et al concluded that in edentulous patient there is a 1.8 fold increase chance of CVD (Elter, 2004). These important studies shed a new light on the association between CVD and periodontal disease. More studies will be required to elucidate mechanism of anti-atherosclerotic events in the reversal of periodontal disease.

Periodontitis and Diabetes Mellitus

Diabetes mellitus is a metabolic disorder which is characterized by hyperglycaemia due to defective secretion of insulin in our body. Diabetes mellitus can be classified into three types according to signs and symptoms: type1, type 2, and gestational.

Type 1 diabetes mellitus is characterized by the destruction of beta cells within the islet of Langer Hans in the pancreas while type 2 ranges from insulin resistance progressively leading to pancreatic beta cell failure and gestational diabetes is a glucose intolerance that starts during pregnancy. There is a hypothesis that linked chronic subclinical inflammation with insulin resistance developing type 2 diabetes. The triggers of inflammation are numerous which includes oral infections which may cause a cascade of events including increased cytokine production, activation of acute phase protein synthesis and consequent insulin resistance that produces pathogenic changes resulting in type 2 diabetes (Amar, 2003). Periodontal pathogen especially P. gingivalis is an excellent invader in the deep vascular endothelium which results in close associations with periodontium and can be found in pathological vascular plaques (Haraszthy, 2000). Once periodontal pathogens are found in the diabetic host, periodontal infection may aggravate microvascular complications thatcan progress to macrovascular complications in the later stages (Matthews, 2002). Periodontal disease more specifically periodontitis is one of the many complications resulting from type 1 and type 2 diabetes. Various studies have found out a higher prevelance of periodontitis in patients with diabetes than healthy individuals. The more direct relationship is periodontal disease leading to diabetes type 2 and it strengthens the bidirectional relationship between type 1 and type 2 diabetes with periodontitis. In patients with periodontal disease there may be a minimal systemic exposure with the periodontal pathogens which leads to a significant change in plasma levels of cytokines and hormones. CRP and IL-6 appears to be promising inflammatory markers in the association between cardiovascular disease and periodontitis (Yudkin, 1999). There are numerous studies which suggests that treatment of periodontal disease leads to control of diabetes. Grossi et al concluded in his study about the effective control of periodontal infection in the diabetic patients which could reduce the level of advanced glycation end products (AGEs) in the serum (Grossi, 1994). AGEs are known to cause hyperglycaemia which is the complication of diabetes thus the level of glycemic control seems to be a key factor. Prevention and control of periodontal disease must be considered as an integral part of diabetes control. The complication of both type 1 and type 2 diabetes resulted in a long term elevation of blood glucose concentration. Hyperglycemia results in the AGEs (Lalla, 2001), formation. These glycation products makes the endothelial cells and monocytes more susceptible to stimuli that induces the cells to produce inflammatory mediators. However the pathophysiological relationship between diabetes and periodontaldisease occurs through the ability of both conditions to induce an inflammatory response leading to production of inflammatory mediators.

Periodontitis and Adverse Pregnancy Outcomes

There is a growing evidence that infection which arises from a remote place like fetal-placental unit may play a role in preterm term delivery of low birth weight infants and it led to a growing awareness of the potential role of bacterial infections in the body. Risk factors for the pre-term delivery may be the use of alcohol, smoking, low grade socioeconomic status, poor parental care, maternal malnutrition. A growing number of studies showed that there is a positive correlation between the periodontal disease and preterm low birth weight (PLBW) infants (Offenbacher, 2001). Contradictory results revealed in Granada, Spain, where statistically significant relationships were observed between PLBW and maternal periodontal probing (Moreu, 2005). However it is recognized that the maternal infections affect the development of the foetus. Periodontal disease is chronic infections which rises the local and systemic prostaglandins and cytokine levels. Hence maternal periodontal disease may be associated with the PLBW through various mechanisms involving inflammatory mediators or direct bacterial assault on amnion. Various risk factors are there which cause preterm rupture of the amniotic membrane and the factors involves high/low maternal age, overweight

and underweight, parity, primiparous mothers, low socioeconomic status, little or no education, alcohol and drug abuse, hyper-tension, Afro-American ethnicity and genital and urinary tract infections. Smoking is regarded as the most important risk factors for periodontitis as well as preterm delivery. Other highly studied risk factors for PLBW are the genital and urinary tract infections. More localized infections of the genital and urinary tract can prolong the period of gestation (Andrews, 1995 and Gibbs, 1992). Periodontal disease is a highly inflammatory disease caused by anaerobic bacteria. Madianos et al studied on the potential role of maternal infection with specific organisms in both 'red' and 'orange' complexes because these are the two most pathogenic complexes in severe periodontal disease. The highest rate of prematurity is observed in those mothers who are without a protective 'red' complex IgG response coupled with an foetal immunoglobulin IgM response to 'orange' complex bacteria (Madianos, 2001). These data supportthe concept that maternal periodontal infections are prevelantin the absence of protective maternal antibody response and is associated with the systemic distribution of oral organisms to the fetus resulting in preterm delivery. Recently F.nucleatum a gram negative anaerobe ubiquitous to the oral cavity was isolated from the amniotic fluid, placenta, chorioamniotic membrane of women delivering prematurely (Han, 2004). A great deal of evidence supports the scenario of periodontal disease as a treatable condition; thus, a positive correlation between periodontal disease and PLBW should create opportunities to provide better periodontal care for pregnant women.

Periodontitis and Osteoporosis

Bone loss is one of the most significant characteristics in periodontal disease and osteoporosis. Osteopenia leads to reduction in bone volume due to imbalance between bone resorption and bone formation resulting in demineralization resulting in osteoporosis (Wactawski-Wende, 1996). Osteoporosis is characterized by compromised bone strength, predisposing to high risk of fracture. Similarly periodontal disease is characterized by resorption of bone specifically the alveolar bone as well as by the soft tissue attachment loss of the tooth. The underlying mechanism of resorption may be the increased systemic/local osteoclastic activity or by local cellular or cytokine effects. Dense infiltrate of mononuclear leukocytes are found in gingiva including T lymphocytes and monocytes/ osteoclast progenitor cells (Taubman, 2001), during periodontal infection.This cellular interaction between T cells and monocyte/lymphocyte progenitor cells is important for osteoclast formation in periodontitis.Interestingly RANKL m RNA is upregulated in the gingiva of the patients with advanced periodontitis. OPG m RNA is downregulated (Liu, 2003). In a study by Nagasawa et al he demonstrated that OPG m RNA was upregulated by LPS secreted from P gingivalis, A actinomycetemcomitans, shedding a light on how LPS stimulated OPG gets involved in the control of osteoclast formation in the periodontal disease (Nagasawa, 2002). Estrogen deficiency is another dominant pathogenic factor for osteoporosis in patients (Jacobs, 1996). Estrogen, either directly or indirectly, modulates cytokines that are important regulators of bone metabolism and also regulators of the host inflammatory response, such as IL-1 alpha, IL-1 beta, TNF-alpha, and macrophage colony-stimulating factor (M-CSF).Thus, deficiency of estrogen initiates an increase in the number of osteoclasts, driven by the same cytokines that down-regulate osteoblast generation. This promotes an imbalance in bone metabolism, leading to reduced bone mineral density (BMD) (Pacifici, 1998). Periodontal disease also activates the pro-inflammatory response, recruiting cytokines and prostanoids, leading to the activation of osteoclast which induces bone resorption. Some cytokines, like IL-1 beta, TNF-alpha, IL-6, and IL-8, have been found at an increased level in inflamed human gingival tissue, in concentrations capable of inducing bone resorption (Gemmell, 2000). Hence many investigations have found statistically significant correlation between periodontal disease and osteoporosis. Significant advances have been made in determining the relationship between periodontal diseases and osteoporosis further studies are needed to clarify this correlation.

Periodontitis and Alzheimer's Disease

Alzheimer's disease (AD) is one of the leading causes of dementia affecting the elderly. Early onset AD has a genetic cause whereas late onset is believed to be both genetical and environmental. Aging is significant risk factor for AD. High fat diet, hypertension, diabetes, history of trauma and susceptibility genes like APOE are among the predisposing risk factors in AD. Hypothetical belief behind the pathogenesis of AD lies in the peripheral infection which leads to inflammation in the brains causing neurodegeneration (Mc Geer, 2001). Periodontitis is a chronic inflammatory disease resulting in increase of local inflammatory mediators that surrounds the trigeminal cranial nerve endings. It also results in achronic systemic host exposure to pro-inflammatory cytokines. So, hypothetically periodontal derived cytokines reach the brain by both systemic and neural pathways and amplify brain cytokine pool. Periodontal pathogens associated with moderate to severe periodontitis are capable of invading tissues. T. denticola is from the family of T. pallidum, which can invade the brain and are found in trigeminal ganglia, brain stem and cortex of human brain. Inflammation is a prominent component of both AD and periodontal disease. Hyperinflammatory genotypes as evidenced by IL-1α-889 AND IL- 1 β +3953 have been associated with both AD and periodontitis. Offenbacher (Offenbacher, 1996) and Mc Geer (Mc Geer, 2001) in the literatures have suggested that an inflammatory trait is characterized by an inflammatory response to an injurious stimulus might result in disease initiation and progression. The significance of the possible involvement of periodontitis in AD onset and progression is that periodontitis is a treatable disease therefore periodontitis is a modifiable risk factor for AD.

Conclusion

Periodontal disease is a global disease which is prevelant for centuries of the very existence of human life on earth. Researcher and clinicians are focusing on the treatment, and development of many scientific tools and pharmaceutical methods, for periodontal disease. Systemic diseases are related to periodontal diseases which are well illustrated in this article and this relations are allowing the developers to have a well proportionate view on the overall distribution of the diseases. Developments of the treatment of the systemic conditions may rely upon the periodontal therapy or vice-versa. So human diseases are now well understood under the light of the disease

relationship and in the future it will aid in the betterment of human civilization on mother earth.

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