ejpmr, 2018,5(9), 189-193

SJIF Impact Factor 4.897

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

ASSOCIATION OF PERIODONTAL INFECTIONS AND SYSTEMIC DISEASES: A REVIEW

***Dr. Ritu Phogat[1], Dr. Manjunath BC[2], Dr. Adarsh Kumar[3], Dr. Meenakshi Malik[4] and Ms. Reena[5]**

[1]Postgraduate Student, Department of Public Health Dentistry, Postgraduate Institute of Dental Sciences, Pt. B.D Sharma University of Health Sciences, Rohtak, Haryana, India.
[2]Senior Professor and Head, Department of Public Health Dentistry, Postgraduate Institute of Dental Sciences, Pt. B.D Sharma University of Health Sciences, Rohtak, Haryana, India.
[3]Associate Professor, Department of Public Health Dentistry, Postgraduate Institute of Dental Sciences, Pt. B.D Sharma University of Health Sciences, Rohtak, Haryana, India.
[4]Research scientist**,** Postgraduate Institute of medical education and research, Chandigarh, India.
[5]Postgraduate student, Department of Pharmaceutical Biotechnology, Jamia Hamdard university, new Delhi, India.

***Corresponding Author: Dr. Ritu Phogat**
Postgraduate Student, Department of Public Health Dentistry, Postgraduate Institute of Dental Sciences, Pt. B.D Sharma University of Health Sciences, Rohtak, Haryana, India.

Article Received on 21/06/2018 **Article Revised on 11/07/2018** **Article Accepted on 31/07/2018**

ABSTRACT

An individual can't have general well-being without healthy periodontium. However, periodontal diseases are very common in developing and developed countries and periodontal infections are increasingly associated with systemic diseases. We aimed to evaluate the current literature on the association between periodontal infections and systemic diseases based on hill's criteria's. We searched the electronic database pubmed and google scholar over a time period of 20-year for studies on periodontal diseases and how they are associated with various systemic diseases. We examined the strength of association between periodontal disease and each systemic disease based on hills criteria of the dose–response relationship and the biological plausibility. We found that individuals with periodontal disease are at higher risk for adverse medical outcomes including cardiovascular diseases, respiratory infections, adverse pregnancy outcomes and diabetes mellitus. Many recent evidences from cohorts, *in vitro* and animal studies suggest that systemic inflammation due to pathogens associated with periodontal disease may play a role in the initiation and progression of particular systemic diseases. Periodontal infections are therefore considered as a risk factor for particular systemic diseases.

KEYWORDS: Periodontium.

INTRODUCTION

According to world health organization (WHO) 2003 report[1] periodontal diseases contributes significantly to global burden of oral and chronic diseases. Periodontal diseases are common chronic infections that involve destruction of the tooth-supporting apparatus, including the gingiva, the periodontal ligament, and alveolar bone.[2] These diseases are initiated by a local accumulation of bacteria adjacent to the tooth. Periodontal diseases, including gingivitis and periodontitis, can affect one tooth or many teeth and, if left untreated, can lead to tooth loss, particularly in adults. It is one of most common dental condition in adults, and is also one of the most common chronic inflammatory diseases affecting a majority of the population throughout the world in both developing and developed countries. Although plaque is essential for the initiation of periodontal diseases, the majority of the destructive processes associated with these diseases are due to an excessive host response to the bacterial challenge. Therefore, periodontal disease is a multifactorial, complex disease.[3]

The classification was developed at the 1999 international Workshop organized by the American Academy of Periodontology (AAP). The classification of periodontal diseases now includes eight general types[4]:

1. Gingivitis
2. Chronic periodontitis
3. Aggressive periodontitis
4. Periodontitis as a manifestation of systemic diseases
5. Necrotizing periodontal diseases
6. Abscesses of the periodontium
7. Periodontitis associated with endodontic lesions
8. Developmental or acquired deformities and conditions

Gingivitis may or may not progress to periodontitis, which is associated with attachment and alveolar bone loss. Periodontal disease is initiated by a local accumulation of bacteria (i.e., dental plaque adjacent to the tooth) and their metabolic products (e.g., endotoxin).

It has been evident that periodontal pathogens like *Porphyromonas gingivalis* can invade the epithelium of gingival tissues.[5] Through this invasion they can reach to systemic circulation of body. Associations have been reported between periodontal disease and cardiovascular disease (CVD), stroke, diabetes, preterm low birth-weight babies, respiratory infections etc.[6,8]

The nine "aspects of association" that Hill discussed in his address (strength of association, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment, and analogy) have been used to evaluate countless hypothesized relationships between risk factors and diseases outcome.[9] We aimed at evaluating relationship of periodontal infections and systemic disease bases on these hills criteria's of association.

Method

We searched the electronic database Pubmed and google scholar from 1997 through 2017 (both years included) for English language articles using the following search terms: 'Periodontal disease and systemic diseases', 'periodontal disease and atherosclerosis', '*P. gingivalis* and cardiovascular diseases', 'periodontal disease and stroke', 'periodontitis and respiratory infections', 'periodontal disease and diabetes mellitus', 'periodontal infections and rheumatoid arthritis' and 'periodontal infections and preterm low birth weight babies'. We selected and reviewed longitudinal, cohort, *in vitro* and animal studies and meta-analysis that provided information related to periodontal infection and systemic diseases.

Periodontal diseases and cardiovascular diseases

A meta-analysis conducted by Alessandra Blaizot et.al (2009)[10] to see the relationship between periodontal diseases and cardiovascular diseases. They analysed 215 epidemiological studies, 47 were observational, of which 29 articles could be combined by the meta-analysis methodology.

The pooled odds ratio calculated from the 22 case-control and cross-sectional studies was 2.35 (95% CI [1.87; 2.96], p< 0.0001). The risk of developing cardiovascular disease was found to be significantly (34%) higher in subjects with periodontal disease compared to those without periodontal disease (pooled relative risk from the 7 cohort studies was 1.34 (95% CI [1.27; 1.42], p< 0.0001). They concluded that from observational studies the subjects with periodontal diseases have higher odds and higher risks of developing cardio-vascular diseases but the reduction in the risk of cardiovascular events associated with the treatment of periodontitis remains to be investigated.

Periodontal diseases and stroke

There are various studies which evident the correlation between periodontal disease and stroke.[11,14]

Strength of association

In a case–control study by Pradeep AR et.al (2009)[11] found that periodontitis (clinical attachment loss [CAL] >6 mm) was found to be significantly associated with haemorrhagic stroke (odds ratio [OR] 2.5, 95% CI 1.1–5.6), but this association did not exhibit a dose-dependent response for periodontitis. Findings from an Indian study showed that a probing pocket depth (PPD) of >4.5 mm was the most significant risk factor for stroke (OR 8.5, 95% CI 1.1–68.2) followed by hypertension (OR 7.6, 95% CI 3.3–17.1) and smoking (OR 3.1, 95% CI 1.3–7.4).

Biological plausibility

Periodontal infections which are associated with systemic inflammation characterized by an increased burden of periodontal pathogens, antigens, endotoxins and liberation of pro-inflammatory cytokines, which may contribute to atherogenesis and thrombo-embolic events culminating in ischaemic stroke.[12,14]

Periodontal diseases and low birth-weight and preterm babies

There are prospective cohort studies, case–control studies and cross-sectional observational studies have correlated poor maternal periodontal health with low birth-weight (LBW) and preterm babies.[15,16]

Strength of association

A case–control study by Pitiphat et.al (2008)[15] found that the OR associated with periodontitis was 1.74 (95% CI 0.65–4.66) for preterm delivery and 2.11 (95% CI 0.76–5.86) for small-for gestational age (SGA) babies. When preterm delivery and/or SGA were combined, the OR was 2.26 (95% CI 1.05–4.85). Another case–control study found that maternal periodontitis was associated with preterm birth (OR 1.77, 95% CI 1.12–2.59), LBW (OR 1.67, 95% CI 1.11–2.51) and intrauterine growth restriction (OR 2.06, 95% CI 1.07–4.19). A meta-analysis by Khader and Ta'ani (2005)[16] showed that pregnant women with periodontal disease had an overall adjusted risk of preterm birth that was 4.28 (95% CI 2.62–6.99) times more than that of healthy subjects. The overall adjusted OR of preterm LBW was 5.28 (95% CI 2.21–12.62), while the overall adjusted OR of a preterm delivery or LBW was 2.3 (95% CI 1.21–4.38).

Dose–response relationship

The severity of periodontitis may adversely affect pregnancy outcomes in a dose-dependent manner. One report suggested that the average PPD and average CAL were significantly higher among women who gave birth to preterm LBW babies.[16] The extent and severity of periodontal diseases appeared to be associated with increased odds of preterm LBW delivery. Larger studies are needed before one can be sure that periodontal infection is a true risk factor for preterm LBW.

Biological plausibility

Chronic infections during pregnancy are associated with premature labour. Periodontal infection may lead to systemic inflammation, which is associated with an increase in CRP levels. Very high CRP levels in early pregnancy have been found to be associated with preterm delivery.[17] The response of the mother's immune system to infection by these periodontal pathogens brings about the release of inflammatory mediators which may trigger preterm labour or result in LBW infants.[18] *P. gingivalis* and *Fusobacterium nucleatum* may colonize placental tissue and contribute to preterm delivery. Studies in animals have shown that these microorganisms can invade maternal and foetal tissues resulting in chorio-amnionitis and placentitis.[19,20]

Periodontal diseases and respiratory diseases

Strength of association

In a systematic review, Azarpazhooh and Leake[21] showed evidence of association of pneumonia with oral health (OR 1.2–9.6) but a weak association (OR< 2.0) between COPD and oral health. The review showed good evidence that improved oral hygiene and frequent professional oral healthcare reduces the progression or occurrence of respiratory diseases among high-risk elderly adults living in nursing homes, especially those in intensive care units (relative risk reduction 34%–83%).

Biological plausibility

It has been reported that dental plaque may act as a reservoir for respiratory pathogens such as *Staphylococcus aureus, Pseudomonas aeruginosa, P. gingivalis, A. actinomycete-mcomitans* and enteric species, and thus be an important risk factor for various respiratory infections.[22] Enzymes released from oral bacteria may act on the respiratory mucosal surface promoting adhesion and colonization of respiratory pathogens. In addition, oral bacterial products in oro-pharyngeal aspirates may stimulate cytokine production from the respiratory epithelial cells, resulting in recruitment of inflammatory cells. The resulting inflamed epithelium may be more susceptible to respiratory infection.[23]

Periodontal diseases and diabetes mellitus

The association of periodontal infections and diabetes mellitus is bidirectional. Various oral conditions are associated with diabetes such as dry mouth, candidal infections, delayed wound healing and periodontal disease. Periodontitis has been described as the sixth complication of diabetes, together with retinopathy, nephropathy, neuropathy, macrovascular disease and altered wound healing.[24, 25]

Poorly controlled diabetes is also associated with periodontal diseases.[26,27] Severe periodontitis in people with diabetes increases the risk of poor glycaemic control due to release of pro-inflammatory cytokines such as TNF-α, which are known to play a role in inducing insulin resistance in a manner similar to that of obesity.[28] Based on their systematic review, Taylor and Borgnakke[29] concluded that periodontitis poses an increased risk for worsening glycaemic control. The risk of developing ketoacidosis, retinopathy and neuropathy is also higher among people who have diabetes and periodontitis.

Dose–response relationship

Chronic periodontitis may have an effect on insulin resistance, since increased levels of TNF-α are seen in patients with severe periodontitis. In chronic periodontitis, there is persistent release of lipo-polysachharides (LPS) from *P. gingivalis* and prolonged up-regulation of TNF-α, which may increase the severity of diabetes.[29] A chronic increase in serum TNF-α due to periodontal infection may actually cause type 2 diabetes as insulin resistance increases, and the patient can no longer metabolize glucose appropriately.[31] Taylor *et al*.[32] found that patients with severe periodontitis had an increased risk of developing poor glycaemic control over time.

Biological plausibility

There is no clear evidence of a causal association between periodontitis and diabetes, but severe periodontal disease increases the severity of diabetes mellitus and complicates metabolic control. Microorganisms that cause periodontitis and the host inflammatory response to these may increase insulin resistance in people with diabetes. This process may be reversed following treatment for periodontitis.[33] Studies have reported that periodontal diseases lead to a significant increase in glycated haemoglobin (HbA1c) and high sensitivity.

CRP, which may be associated with poor glycaemic control.[34,35] The virulence of *P. gingivalis* is also one of the factors associated with poor glycaemic control. These host–bacterial interactions produce a resultant impact on various systems in the human body including rheumatoid arthritis.

CONCLUSION

Periodontal disease is possibly an important risk factor for various systemic diseases. World health organization suggested a common risk factor approach to tackle chronic diseases and periodontal diseases. Based on the common risk factors approach, improvements in periodontal health may be achieved by countries along with a better control of chronic health conditions such as diabetes mellitus, and intervention in relation to tobacco use, alcohol consumption, and unhealthy diet. Maintenance of good oral health should be given priority. People should be educated on the importance of good oral health and the risks associated with poor oral health. Dentists and medical practitioners should work together to provide comprehensive healthcare, thereby reducing the morbidity and mortality associated with periodontal infections.

Conflict of interest: None.

REFERENCES

1. Peterson PE, Ogawa H. strengthening the prevention of periodontal diseases: the WHO approach. Journal of periodontology, 2005 Dec.; 76(12): 2187-93.
2. Armitage GC. Periodontal diseases: diagnosis. Ann Periodontol, 1996; 1: 37–215.
3. Mariotti A. Dental plaque-induced gingival diseases. Annals of periodontology, 1999 Dec. 1; 4(1): 7-17.
4. Armitage GC. Development of a classification system for periodontal diseases and conditions. Annals of periodontology, 1999 Dec. 1; 4(1): 1-6.
5. Newman M, Carranza's Clinical Periodontology, 10th edition, Singapur: W.B saunders company, 1998.
6. Potempa J, Mydel P, Koziel J. The case for periodontitis in the pathogenesis of rheumatoid arthritis. Nature Reviews Rheumatology, 2017 Aug. 24.
7. Kim J, Amar S. Periodontal disease and systemic conditions: a bidirectional relationship. Odontology, 2006 Sep. 1; 94(1): 10-21.
8. Manjunath BC, Praveen K, Chandrashekar BR, Rani RM, Bhalla A. Periodontal infections: A risk factor for various systemic diseases.
9. Hill AB. The environment and disease: association or causation? Proc R Soc Med., 1965; 58: 295–300.
10. Blaizot A, Vergnes JN, Nuwwareh S, Amar J, Sixou M. Periodontal diseases and cardiovascular events: meta-analysis of observational studies. International dental journal, 2009 Aug. 1; 59(4): 197-209.
11. Pradeep AR, Hadge P, Arjun Raju P, Shetty SR, Shareef K, Guruprasad CN. Periodontitis as a risk factor for cerebrovascular accident: a case–control study in the Indian population. Journal of periodontal research, 2010 Apr. 1; 45(2): 223-8.
12. Grau AJ, Becher H, Ziegler CM, Lichy C, Buggle F, Kaiser C, Lutz R, Bültmann S, Preusch M, Dörfer CE. Periodontal disease as a risk factor for ischemic stroke. Stroke, 2004 Feb. 1; 35(2): 496-501.
13. Joshipura KJ, Hung HC, Rimm EB, Willett WC, Ascherio A. Periodontal disease, tooth loss, and incidence of ischemic stroke. Stroke, 2003 Jan. 1; 34(1): 47-52.
14. Offenbacher S, Boggess KA, Murtha AP, Jared HL, Lieff S, McKaig RG, Mauriello SM, Moss KL, Beck JD. Progressive periodontal disease and risk of very preterm delivery. Obstetrics & Gynecology, 2006 Jan 1; 107(1): 29-36.
15. Pitiphat W, Joshipura KJ, Gillman MW, Williams PL, Douglass CW, Rich-Edwards JW. Maternal periodontitis and adverse pregnancy outcomes. Community dentistry and oral epidemiology, 2008 Feb. 1; 36(1): 3-11.
16. Khader YS, Ta'ani Q. Periodontal diseases and the risk of preterm birth and low birth weight: a meta-analysis. Journal of periodontology, 2005 Feb. 1; 76(2): 161-5.
17. Khader Y, Al-shishani L, Obeidat B, Khassawneh M, Burgan S, Amarin ZO, Alomari M, Alkafajei A. Maternal periodontal status and preterm low birth weight delivery: a case–control study. Archives of gynecology and obstetrics, 2009 Feb. 1; 279(2): 165.
18. Madianos PN, Lieff S, Murtha AP, Boggess KA, Auten Jr RL, Beck JD, Offenbacher S. Maternal periodontitis and prematurity. Part II: Maternal infection and fetal exposure. Annals of Periodontology, 2001 Dec. 1; 6(1): 175-82.
19. Bélanger M, Reyes L, Von Deneen K, Reinhard MK, Progulske-Fox A, Brown MB. Colonization of maternal and fetal tissues by Porphyromonas gingivalis is strain-dependent in a rodent animal model. American journal of obstetrics and gynecology, 2008 Jul 31; 199(1): 86-e1.
20. Han YW, Redline RW, Li M, Yin L, Hill GB, McCormick TS. Fusobacterium nucleatum induces premature and term stillbirths in pregnant mice: implication of oral bacteria in preterm birth. Infection and immunity, 2004 Apr. 1; 72(4): 2272-9.
21. Azarpazhooh A, Leake JL. Systematic review of the association between respiratory diseases and oral health. Journal of periodontology, 2006 Sep.; 77(9): 1465-82.
22. Sumi Y, Miura H, Michiwaki Y, Nagaosa S, Nagaya M. Colonization of dental plaque by respiratory pathogens in dependent elderly. Archives of gerontology and geriatrics, 2007 Apr. 30; 44(2): 119-24.
23. Didilescu AC, Skaug N, Marica C, Didilescu C. Respiratory pathogens in dental plaque of hospitalized patients with chronic lung diseases. Clinical oral investigations, 2005 Sep. 1; 9(3): 141-7.
24. Löe H. Periodontal disease: the sixth complication of diabetes mellitus. Diabetes care., 1993 Jan 1; 16(1): 329-34.
25. Mealey BL, Oates TW. Diabetes mellitus and periodontal diseases. Journal of periodontology, 2006 Aug; 77(8): 1289-303.
26. Taylor GW. Bidirectional interrelationships between diabetes and periodontal diseases: an epidemiologic perspective. Annals of periodontology, 2001 Dec. 1; 6(1): 99-112.
27. Nishimura F, Murayama Y. CONCISE REVIEW biological: Periodontal inflammation and insulin resistance—lessons from obesity. Journal of dental research, 2001 Aug; 80(8): 1690-4.
28. Tsai C, Hayes C, Taylor GW. Glycemic control of type 2 diabetes and severe periodontal disease in the US adult population. Community dentistry and oral epidemiology, 2002 Jun 1; 30(3): 182-92.
29. Taylor GW, Borgnakke WS. Periodontal disease: associations with diabetes, glycemic control and complications. Oral diseases, 2008 Apr 1; 14(3): 191-203.
30. Wang PL, Ohura K. Porphyromonas gingivalis lipopolysaccharide signaling in gingival fibroblasts–

CD14 and Toll-like receptors. Critical Reviews in Oral Biology & Medicine, 2002 Mar; 13(2): 132-42.
31. Lazenby MG, Crook MA. The innate immune system and diabetes mellitus: the relevance of periodontitis? A hypothesis. Clinical Science, 2010 Nov 1; 119(10): 423-9.
32. Taylor GW, Burt BA, Becker MP, Genco RJ, Shlossman M, Knowler WC, Pettitt DJ. Severe periodontitis and risk for poor glycemic control in patients with non-insulin-dependent diabetes mellitus. Journal of periodontology, 1996 Oct; 67(10s): 1085-93.
33. Nishimura F, Iwamoto Y, Mineshiba J, Shimizu A, Soga Y, Murayama Y. Periodontal disease and diabetes mellitus: the role of tumor necrosis factor-α in a 2-way relationship. Journal of Periodontology, 2003 Jan 1; 74(1): 97-102.
34. Lim LP, Tay FB, Sum CF, Thai AC. Relationship between markers of metabolic control and inflammation on severity of periodontal disease in patients with diabetes mellitus. Journal of Clinical Periodontology, 2007 Feb. 1; 34(2): 118-23.
35. Makiura N, Ojima M, Kou Y, Furuta N, Okahashi N, Shizukuishi S, Amano A. Relationship of Porphyromonas gingivalis with glycemic level in patients with type 2 diabetes following periodontal treatment. Molecular Oral Microbiology, 2008 Aug. 1; 23(4): 348-51.