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Review Article

Mouth: A portal to the body

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ABSTRACT

Periodontal disease is now increasingly believed to play a significant part in various systemic conditions. Likewise these systemic diseases and their severity have been found to have an impact on the morbidity of periodontal disease. A number of mechanisms specific to such interlink have been proposed and later established in numerous studies. The disorders with such bidirectional link with periodontal disease include cardiovascular, respiratory, neurological, and connective tissue diseases. The periodontal – systemic interlink has a vibrant effect on the management aspects and is of paramount topical interest to clinicians. We review the pertaining literature (Google scholar and pubmed).

Key Words: Inter-link, periodontal disease, systemic

INTRODUCTION

Periodontal disease and the systemic interlink, although well researched in the scientific community, is not universally cognizant among clinicians. There is a dire need to bring the awareness about the inter-relationship as it has far-reaching effects on management aspects. Periodontitis as a manifestation of systemic diseases is one of the seven categories of periodontitis as defined by the American Academy of Periodontology (1999) classification system.¹ The association of periodontitis between various systemic diseases is explained by decreased host resistance to infections or dysfunction in the connective tissue of the gums and/or increasing patient susceptibility to inflammation-induced destruction. A literature review (Google scholar and pubmed) of evidence-based associations between periodontal disease and various systemic disorders is presented.

PERIODONTAL DISEASE AND DIABETES

There is abundant evidence that diabetes increases the risk of periodontal disease and likewise the latter has shown to increase insulin resistance thereby perturbing glycemic control.

In diabetes, impaired neutrophil function may undermine the eradication of bacteria in the periodontal pocket, leading to periodontal inflammation and destruction. The key factors behind such impairment such as monocyte upregulation and stimulation of NF-κB may be secondary to AGE (advanced glycation end products) and R (receptor)-AGE reciprocity.² In a study, it was shown that the oxidative stress in periodontitis compounds the release of proinflammatory cytokines such as interleukin-1beta (IL-1β), and IL-6 and tumor necrosis factor-alpha (TNF-α).³ The degree of glycemic control has also shown to correlate with the severity of epiderdonitis. Periodontitis-affected diabetes patients having HbA1c levels more than 8% demonstrate twice the normal levels of IL-1β in gingival crevicular fluid.⁴

Known to have a bidirectional relationship, periodontitis predisposes to increased levels of inflammatory markers such as matrix
metalloproteinases (MMP), TNF-α, IL-1β, IL-6 and prostaglandin E1 in diabetes.[5] The effect of adequate periodontal therapy on glycemic control was studied and it was concluded that the therapy correlated with definite improvement in mean HbA1c values (from 8% to 7.1%), in levels of TNF-α and fasting insulin.[6] Likewise those with HbA1c levels greater than 9% sported severe periodontitis with higher probing pocket depths and more sites with loss of attachment than those with lesser HbA1c levels.[7]

Insulin resistance is believed to be perpetuated by fibrinogen, C-reactive protein, and plasminogen activator inhibitor-1.[8] Diabetics also manifest perturbed pH of saliva and its buffering capacity, levels, and activity of peroxidase, increased incidence of dry mouth, need for the prevention of caries and prosthetic corrections.[9,10]

PERIODONTAL DISEASE AND CARDIOVASCULAR DISEASE

Periodontal disease is an established risk factor conferring about 24-35% increase in the risk of coronary heart disease (CHD).[11]

Bacterial lipopolysaccharide, cytokines, and mechanical stress may ensue a cross-reactivity of antibodies to major antigens of periodontopathic bacteria, mainly bacterial heat shock protein (HSP-GroEL) on endothelial cells resulting in endothelial dysfunction and atherosclerosis. Risk factors such as high blood cholesterol are known to aggravate progression from early fatty streak lesions to severe and irreversible atherosclerosis. High anti-HSP60/65 antibody titres correlated with high morbidity and mortality due to atherosclerosis.[12] Major periodontal pathogens like Aggregatibacter actinomycetemcomitans and Porphyromonas gingivalis have shown clear associations with future stroke,[13] increased risk of myocardial infarction,[14] and acute coronary syndrome.[15] Periodontitis-induced elevation of serum pro-inflammatory cytokines, inflammatory biomarkers, and serum LDL/triglycerides may damage vascular endothelial cells, leading to recruitment of macrophages or foam cell formation and development of atheromatous plaques. Increasing evidence confirms that periodontitis facilitates atheroma formation.[16]

In a study, periodontal disease severity correlated to the angiographic extent of coronary lesions. The mean periodontal pocket depth was greater in patients with CHD and correlated with high sensitivity C reactive protein (hs-CRP), serum amyloid A protein, and fibrinogen suggesting systemic inflammatory response.[17] Common cardio-metabolic risk factors including body weight,[18] dyslipidemia,[19] and hypertension[20] are associated with increased odds of prevalence of periodontitis.[21] Periodontal disease is an important factor in determining recurrent cardiovascular events in myocardial infarction.[22]

In the periodontitis and vascular events (PAVE) pilot study, consideration of any preventive or periodontal care compared to no treatment showed a significant reduction in the percentage of people with elevated hs-CRP (values >3 mg/l).[23] Intense periodontal therapy, including full-mouth subgingival debridement and locally delivered antibiotics is shown to significantly improve flow-mediated dilatation beyond 60 days which correlates to the degree of improvement in the periodontal parameters.[24] Another study showed improved intima medial thickness 12 months after periodontal therapy.[25]

PERIODONTAL DISEASE AND STROKE

The plethora of factors that interplay between periodontal disease and cardiovascular disease and diabetes may play a similarly important role in the causation of stroke. A study that analyzed dental radiographs dated prior to stroke showed that being in the upper tertile of percent of sites with bone loss ≥2 mm was associated with higher risk for ischemic stroke.[26]

FDG (fluorodeoxyglucose)-PET measurements of metabolic activity within periodontal tissue showed a strong relationship between periodontal target to background ratio and histologically assessed inflammation with macrophage infiltration within excised carotid artery plaques.[27] REGARDS (reasons for geographic and racial differences in stroke) study showed that periodontal disease resulting in tooth loss was associated with inflammatory markers and stroke.[28] Advanced periodontitis or edentulousness apart from being an independent risk factor for greater National Institute of Health stroke scale (NIHSS) score on admission correlated with greater neurological deficit on admission and worse outcome at hospital discharge.[29]
PERIODONTAL DISEASE AND KIDNEY DISEASE

Periodontal disease and edentulousness have shown association with chronic kidney disease (CKD). There is a bidirectional relationship between CKD and periodontal disease, mediated by hypertension and the duration of diabetes. Compared with mild or no periodontal disease, moderate-to-severe disease (2 or more teeth with at least 6 mm of inter-proximal attachment loss) was significantly associated with death from cardiovascular causes in a study on CKD patients on hemodialysis. Another large study showed that edentulousness and low serum titer to A. actinomycetemcomitans could be risk indicators for CKD.

Periodontitis is shown to be a risk factor for the development of overt nephropathy and end-stage renal disease (ESRD). In a study, macroalbuminuria was 2.0, 2.1, and 2.6 times greater and the incidence of ESRD was also 2.3, 3.5, and 4.9 times greater in individuals with moderate or severe periodontitis or in those who were edentulous, respectively, than those with none/mild periodontitis.

PERIODONTAL DISEASE AND PREGNANCY

Moderate/severe periodontal disease is associated with elevated C-Reactive protein (CRP) levels early in pregnancy. Periodontal disease has been associated with adverse pregnancy outcomes such as preeclampsia, low birth weight (LBW), preterm birth, miscarriages between 12 and 24 weeks of gestation, decreased average newborn birth weight or gestational age, and fetal growth restriction. In a study, treatment with scaling and/or root planning during pregnancy significantly reduced preterm birth and resulted in borderline significant lowering of LBW infant incidence.

PERIODONTAL DISEASE AND LUNG DISEASE

The relationship between periodontitis and lung disease has been well studied. Cariogenic bacteria and periodontal pathogens in saliva or dental plaque are found to be risk factors for aspiration pneumonia in nursing home patients. Chronic obstructive pulmonary disease (COPD) patients are more likely to have fewer teeth and a higher plaque index than controls. Inappropriate tooth brushing method, lower regular supra-gingival scaling and poorer oral health knowledge are known to be significantly associated with COPD. A study showed that the prevalence of chronic marginal periodontitis (general marginal bone level ≥4 mm) is significantly higher in COPD patients compared to controls (44% vs. 7.3%). This association appears to be independent of risk factors for periodontitis such as age, pack years smoked, body mass index, use of corticosteroids, and bone mineral density. COPD patients also sport a significantly higher average loss of attachment (5.72 ± 0.8 mm vs. 3.92 ± 0.5 mm) and bleeding on probing (86 ± 12% vs. 71 ± 16%) compared to controls.

PERIODONTAL DISEASE AND OTHER DISORDERS

A study found that when compared to the lowest tertile of etiologic bacterial burden (subgingival periodontal bacteria), the highest had higher prevalent hypertension, systolic blood pressure (BP) 9 mmHg higher, and diastolic BP 5 mmHg higher. Association of periodontal disease with rheumatoid arthritis (RA) has been found and treatment of the former resulted in reduced severity of active RA. Ankylosing spondylitis is also known to significantly increase the risk of periodontal disease. Osteoporosis is noted to exhibit higher clinical attachment loss (AL) ≥6 mm and interproximal gingival recession (GR) ≥5 mm.

DISCUSSION

Many systemic diseases are believed to be affected by periodontal disease and the association may be bidirectional in some. Management of these entities may need to target periodontal disease. Thorough patient education and improved motivation for following guidelines and follow-up and regular assessment by clinicians working as a team (physicians/specialists/dentists etc) will ensure improved health of various systems as a whole.

The inter-link between periodontitis and various diseases discussed above has not been unanimously and universally established in all the studies. An older study established no significant radiographic evidence of periodontitis in a study on diabetics with considerable dysglycemia of long duration. Likewise another study on diabetics with significant dysglycemia showed no significant evidence of periodontitis.
periodontal disease found no demonstrable improvement in glycemic control up on reception of nonsurgical periodontal therapy including root planning.\(^\text{[48]}\) A similar lack of improvement in glycemic control was found in another study done on diabetics who underwent periodontal therapy for 4 months.\(^\text{[49]}\)

A large prospective cohort study did not find convincing evidence of a causal association between periodontal disease and CHD risk.\(^\text{[50]}\) Pregnant subjects with periodontal disease were assessed for the risk of adverse pregnancy outcomes such as preterm birth, preeclampsia, fetal growth restriction, or perinatal death and no association was found with periodontal disease.\(^\text{[51]}\) A multicenter, randomized clinical trial on pregnant subjects with periodontal disease compared scaling and root planning to tooth polishing and found no association with the occurrence of spontaneous preterm birth at <35 weeks of gestation.\(^\text{[52]}\)

A clear relationship between periodontitis and respiratory infectious diseases such as bacterial pneumonia and bronchitis has not been established.\(^\text{[53]}\) An epidemiologic study found no association between periodontal state or poor oral hygiene and acute respiratory disease in the community-dwelling population.\(^\text{[54]}\)

Most systemic conditions like diabetes, CHD, CKD, etc., may stem from multifactorial etiologies. Periodontal disease may act as a modifying factor in conjunction with the variety of factors influencing the outcome of systemic diseases. The degree and extent of periodontal disease may be different in the subsets of patients with these systemic diseases and may help explain the non-universality of such an inter-link.

**CONCLUSION**

As depicted by a few studies that questioned the association, we need to keep in mind that those with adequately managed systemic diseases do not guarantee a healthy periodontium and vice versa. Treating periodontal infection may have promising practical advantages that translate into better management of systemic diseases. In specifically those diseases that demonstrate bidirectional association, adequately treated systemic diseases mirror improved oral hygiene and minimize periodontal disease morbidity. Universal management protocol and guidelines may necessitate further exploratory studies into this interlink but it is evident that in battling systemic disease and periodontal disease, taking into account the contribution of each to one another, shall bolster our approach in bettering the all-round health.

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**REFERENCES**

1. Armitage GC. Periodontal diagnoses and classification of periodontal diseases. Periodontol 2000 2000;34:9-21.
2. Southerland JH, Taylor GW, Offenbacher S. Diabetes and Periodontal Infection: Making the Connection. Clin Diabetes 2005;23:4171-8.
3. Taylor GW, Borgnakke WS. Periodontal disease: Associations with diabetes, glycemic control and complications. Oral Dis 2008;14:191-203.
4. Engebretson SP, Hey-Hadavi J, Ehrhardt FJ, Hsu D, Celenti RS, Grbic JT, et al. Gingival crevicular fluid levels of interleukin-1beta and glycemic control in patients with chronic periodontitis and type 2 diabetes. J Periodontol 2004;75:1203-8.
5. Beklen A, Ainola M, Hukkanen M, Gürçan C, Sorsa T, Konttinen YT. MMPs, IL-1, and TNF are regulated by IL-17 in periodontitis. J Dent Res 2007;86:347-51.
6. Iwamoto Y, Nishimura F, Nakagawa M, Sugimoto H, Shikata K, Makino H, et al. The effect of antimicrobial periodontal treatment on circulating tumor necrosis factor alpha and glycated hemoglobin level in patients with type 2 diabetes. J Periodontol 2001;72:774-8.
7. Tsai C, Hayes C, Taylor GW. Glycemic control of type 2 diabetes and severe periodontal disease in the US adult population. Community Dent Oral Epidemiol 2002;30:182-92.
8. Festa A, D’Agostino R Jr, Tracy RP, Haffner SM; Insulin Resistance Atherosclerosis Study. Elevated levels of acute-phase proteins and plasminogen activator inhibitor-1 predict the development of type 2 diabetes: The insulin resistance atherosclerosis study. Diabetes 2002;51:1131-7.
9. Sandberg GE, Sundberg HE, Fjellstrom CA, Wikblad KF. Type 2 diabetes and oral health: A comparison between diabetic and non-diabetic subjects. Diabetes Res Clin Pract 2000;50:27-34.
10. Aren G, Sepet E, Ozdemir D, Dinççağ N, Güvener B, Firatli E. Periodontal health, salivary status, and metabolic control in children with type 1 diabetes mellitus. J Periodontol 2003;74:1789-95.
11. Janket SJ, Baird AE, Chuang SK, Jones JA. Meta-analysis of periodontal disease and risk of coronary heart disease and stroke. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2003;95:173-9.
12. Taylor GW, Borgnakke WS. Periodontal disease: Associations with diabetes, glycemic control and complications. Oral Dis 2008;14:191-203.
13. Pussinen PJ, Alfthan G, Joussilahti P, Paju S, Tuomilehto J. Systemic exposure to Porphyromonas gingivalis predicts incident stroke. Atherosclerosis 2007;193:222-8.
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14. Pusseinnen PJ, Alfhath G, Tuomilehto J, Asikainen S, Jousilahti P. High serum antibody levels to Porphyromonas gingivalis predict myocardial infarction. Eur J Cardiovasc Prev Rehabil 2004;11:408‑11.

15. Renvert S, Pettersson T, Ohlsson O, Persson GR. Bacterial profile and burden of periodontal infection in subjects with a diagnosis of acute coronary syndrome. J Periodontol 2006;77:1110‑9.

16. Gapski R, Cobb CM. Chronic inflammatory periodontal disease. A risk factor for cardiovascular disease and ischemic stroke? Grand Rounds in Oral‑Sys Med 2006;1:14‑22.

17. Amabile N, Susini G, Pettenati‑Soubayroux I, Bonello L, Gil JM, Arques S, et al. Severity of periodontal disease correlates to inflammatory systemic status and independently predicts the presence and angiographic extent of stable coronary artery disease. J Intern Med 2008;263:644‑52.

18. Kongstad J, Hvidtfeldt UA, Gronbaek M, Stoltze K, Amabile N, Susini G, Pettenati‑Soubayroux I, Bonello L, Gil JM, Arques S, et al. Severity of periodontal disease correlates to inflammatory systemic status and independently predicts the presence and angiographic extent of stable coronary artery disease. J Intern Med 2008;263:644‑52.

19. Saxlin T, Suominen‑Taipale L, Kattainen A, Marniemi J, Knuttila M, Ylöstalo P. Association between serum lipid levels and periodontal infection. J Clin Periodontol 2008;35:1040‑7.

20. Franek E, Klamczynska E, Ganowicz E, Blach A, Budlewski T, Gorska R. Association of chronic periodontitis with left ventricular mass and central blood pressure in treated patients with essential hypertension. Am J Hypertens 2009;22:203‑7.

21. D’Auito F, Sabbah W, Netuveli G, Donos N, Hingorani AD, Deanfield J, et al. Association of the metabolic syndrome with severe periodontitis in a large U.S. population‑based survey. J Clin Endocrinol Metab 2008;93:3989‑94.

22. Dorn JM, Genco RJ, Grossi SG, Falkner KL, Hovey A, D mes PM, Curr Opin Endocrinol Diabetes Obes 2008;15:135‑41.

23. Moore S, Icle M, Coward PY, Randhawa M, Borkowska E, Baylis R, et al. A prospective study to investigate the relationship between periodontal disease and adverse pregnancy outcome. Br Dent J 2004;197:251‑8; discussion 247.

24. Romero BC, Chiquito CS, Elejalde LE, Bernardoni CB. Relationship between periodontal disease in pregnant women and the nutritional condition of their newborns. J Periodontol 2002;73:1177‑83.

25. Polyzos NP, Polyzos IP, Laurina M, Zappad B, Cortinovis I, et al. Effect of periodontal disease treatment during pregnancy on preterm birth incidence: A metaanalysis of randomized trials. Am J Obstet Gynecol 2009;200:225‑32.

26. Pajru S, Scannapieco FA. Oral biofilms, periodontitis, and pulmonary infections. Oral Dis 2007;13:508‑12.

27. Wang Z, Zhou X, Zhang J, Zhang L, Song Y, Hu FB, et al. Periodontal disease adversely affects the nutritional condition of their newborns. J Periodontol 2007;78:1177‑83.
44. Ortiz P, Bissada NF, Palomo L, Han YW, Al-Zahrani MS, Panneerselvam A, et al. Periodontal therapy reduces the severity of active rheumatoid arthritis in patients treated with or without tumor necrosis factor inhibitors. J Periodontol 2009;80:535-40.
45. Pischon N, Pischon T, Gülmez E, Kröger J, Purucker P, Kleber BM, et al. Periodontal disease in patients with ankylosing spondylitis. Ann Rheum Dis 2010;69:34-8.
46. Shum I, Leung PC, Kwok A, Corbet EF, Orwell ES, Phipps KR, et al. Periodontal conditions in elderly men with and without osteoporosis or osteopenia. J Periodontol 2010;81:1396-402.
47. Barnett ML, Baker RL, Yancey JM, MacMillan DR, Kotoyan M. Absence of periodontitis in a population of insulin-dependent diabetes mellitus (IDDM) patients. J Periodontol 1984;55:402-5.
48. Aldridge JP, Lester V, Watts TL, Collins A, Viberti G, Wilson RF. Single-blind studies of the effects of improved periodontal health on metabolic control in type 1 diabetes mellitus. J Clin Periodontol 1995;22:271-5.
49. Jones JA, Miller DR, Wehler CJ, Rich SE, Kralj-Kaye EA, McCoy LC, et al. Does periodontal care improve glycemic control? The Department of Veterans Affairs Dental Diabetes Study. J Clin Periodontol 2007;34:46-52.
50. Hujoel PP, Drangsholt M, Spiekerman C, DeRouen TA. Periodontal disease and coronary heart disease risk. JAMA 2000;284:1406-10.
51. Srinivas SK, Sammel MD, Stamilio DM, Clothier B, Jeffcoat MK, Parry S, et al. Periodontal disease and adverse pregnancy outcomes: Is there an association? Am J Obstet Gynecol 2009;200:497.e1-8.
52. Macones GA, Parry S, Nelson DB, Strauss JF, Ludmir J, Cohen AW, et al. Treatment of localized periodontal disease in pregnancy does not reduce the occurrence of preterm birth: Results from the Periodontal Infections and Prematurity Study (PIPS). Am J Obstet Gynecol 2010;202:147.e1-8.
53. Scannapieco FA, Papandonatos GD, Dunford RG. Associations between oral conditions and respiratory disease in a national sample survey population. Ann Periodontol 1998;3:251-6.
54. Scannapieco FA, Stewart EM, Mylotte JM. Colonization of dental plaque by respiratory pathogens in medical intensive care patients. Crit Care Med 1992;20:740-5.

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