Periodontal disease and systemic health: An update for medical practitioners
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ABSTRACT

Introduction: Chronic periodontal disease is a highly prevalent dental condition affecting tooth-supporting tissues. Scientific evidence is accumulating on links between periodontal disease and various systemic conditions. This narrative review provides a holistic yet succinct overview that would assist medical practitioners to deliver integrated care for better clinical outcomes.

Method: Scientific evidence on associations between periodontal disease and systemic conditions was synthesised and critically appraised. Key findings of latest prospective cohort studies, randomised clinical trials, and meta-analysis were closely assessed and compiled.

Results: A bidirectional relationship has been established, indicating that diabetes and periodontal disease are closely linked and amplify one another, if not successfully controlled. Existing evidence also supports the associations of periodontal disease with cardiovascular diseases and adverse pregnancy outcomes. Successful treatment of periodontal disease and dental prophylaxis has been shown to improve clinical outcomes in these systemic conditions. Other systemic conditions associated with periodontal disease include respiratory diseases, Alzheimer’s disease, rheumatoid arthritis and chronic kidney disease. Although the underlying mechanisms remain to be fully elucidated, it is generally accepted that the inflammatory burden of chronic periodontal disease has an important systemic impact.

Conclusion: Oral-systemic links are multifaceted and complex. While evidence linking periodontal disease with a variety of systemic conditions is still emerging, the nature of the relationship is becoming clearer. The updated understanding of these associations warrants the attention of medical experts and policymakers for a concerted effort to develop a patient-centric, integrated model for the treatment of comorbid dental and medical conditions.

Keywords: Cardiovascular diseases, dentistry, diabetes, oral health, periodontal diseases, systemic diseases

INTRODUCTION

Care for the oral cavity lies in the intersection of dentistry and medicine. As the oral cavity serves as an entry to the gastrointestinal tract and the point where the digestion process begins, it is often recognised as an important gateway to dietary and nutritional health. Oral health, however, is also relevant to other aspects of general health. A potential impact of oral infections on systemic health was revealed centuries ago when Hippocrates reportedly cured a patient’s rheumatism by pulling out an infected tooth.\textsuperscript{1} Nevertheless, the implications of oral health on general health were not fully appreciated until a sizeable body of scientific evidence in the last 3 decades pointed towards a strong oral-systemic link.\textsuperscript{2,3}

In particular, periodontal disease, a highly prevalent chronic inflammatory disease of tooth-supporting structures,\textsuperscript{4} has been linked to a wide range of common medical conditions.\textsuperscript{5,6} Scientific evidence suggests periodontal disease to be associated with type 2 diabetes mellitus (T2DM),\textsuperscript{7} cardiovascular disease\textsuperscript{6} and adverse pregnancy outcomes,\textsuperscript{9} among others. Due to the large volume of data on oral-systemic links accumulated over the last decades, there is a need to closely assess the evidence, interpret the findings in clinical context, and provide medical practitioners with a holistic yet succinct overview. Hence, this narrative review aims to appraise and synthesise evidence on links between periodontal disease and common medical conditions,
Periodontal and systemic diseases—Ashish Chetan Kalhan et al.

CLINICAL IMPACT

What is New

• Systemic health is closely linked to the state of the oral cavity. Pathologic conditions in the mouth may alter the risk and treatment outcomes of systemic conditions.

Clinical Implications

• Healthcare practitioners are encouraged to proactively engage and educate patients to be more aware of the common signs of periodontal disease and seek necessary dental care in a timely manner.

• As there are common risk factors for periodontal disease and many systemic chronic conditions, medical-dental collaboration for co-management of medical and dental conditions may optimise treatment outcomes, as advocated in some international clinical guidelines.

and provide an update on recent findings reported in literature.

Singapore’s population is rapidly ageing, and the burden of periodontal disease and chronic systemic diseases, such as diabetes and cardiometabolic diseases, are expected to significantly increase in the foreseeable future.10,11 There is a pressing need to address the challenges of prevalent comorbid conditions in order to deliver comprehensive care and improve healthcare outcomes in the Singapore population.

METHOD

Data are compiled from latest prospective cohort studies or randomised controlled trials published from 2000–2021 by searching PubMed, Medline and Google Scholar. Scientific evidence and key findings on associations between periodontal disease and systemic conditions were assessed, synthesised and critically appraised.

RESULTS

Periodontal disease: Pathogenesis and prevalence

Periodontal disease is a chronic inflammatory disease affecting the supporting structures of the teeth. Often referred to as “gum disease”, periodontal disease is, however, not confined to the gums. It is characterised by progressive destruction of the whole periodontium, which comprises both soft and hard tissues (i.e. gingiva, cementum, periodontal ligament and alveolar bone).4

Fig. 1 highlights the clinical signs of various stages of periodontal disease, ranging from gingivitis to mild, moderate and severe periodontitis. The initial stage of periodontal disease, limited to the soft tissue (gums), is called “gingivitis” and is clinically manifested as red/swollen gums that bleed after toothbrushing. In susceptible individuals, dysregulation of inflammatory and immune pathways leads to chronic inflammation and destruction of periodontal tissues, resulting in an advanced form of the disease known as “periodontitis”. Common clinical manifestations of periodontitis include (1) swollen, red gums and periodontal abscesses; (2) disruption of clinical attachment of gums from the tooth surface, resulting in periodontal pockets and receding gums; and (3) tooth migration, tooth mobility and subsequent tooth loss.

Periodontal disease is initiated by uncontrolled inflammatory response to constant colonisation of pathogenic bacteria at the tooth-gum margin.12 Although bacterial infection is a necessary condition, it is the host’s inflammatory response to the microbial challenge that is responsible for the progression of periodontal degradation. Bacterial pathogens trigger the leukocytes of the innate immune system to release pro-inflammatory mediators, such as cytokines, which play an essential role in the progression of periodontal disease. The inflammatory response to periodontal bacteria or their by-products may have systemic effects.13 This seemingly mild, localised periodontal inflammation could trigger a chronic generalised hyperinflammation condition, disrupt the innate and adaptive immune system, and may cause or aggravate other systemic health issues.

Periodontal disease is very common, with severe periodontitis ranked as the world’s 6th most prevalent health condition.14 Around 1.1 billion cases of severe periodontal disease were reported in 2019, equivalent to approximately 15% of the global population.15 In Singapore, a nationwide oral health survey conducted by the Health Promotion Board in 2003 revealed that 8.5 out of 10 adults suffered from mild to moderately severe forms of periodontal disease.16 Another survey led by the Ministry of Community Development, Youth and Sports in 2009 reported that about one-third of community-dwelling older adults were completely toothless (edentulous)17—a surrogate marker for dental caries and periodontal disease, which are the main causes of tooth loss. Periodontitis commonly develops in
the 4th decade of life and its prevalence increases with age. It has been projected that periodontitis will remain a salient health challenge worldwide, especially when more people are able to retain their teeth until later in life.\textsuperscript{14}

**Periodontal disease and diabetes mellitus: A bidirectional relationship**

Among all possible links between oral conditions and general health, the relationship between periodontal disease and T2DM is undoubtedly the most well-established, and attracts the most scholarly and clinical attention. The link between these 2 diseases appears to be a 2-way relationship.\textsuperscript{18} Individuals with periodontal disease exhibited poorer glycaemic control and have 19–33\% higher risk of developing diabetes,\textsuperscript{19} with the highest incidence reported in those with severe periodontal disease.\textsuperscript{20,21} Also, presence of periodontal disease has been found to increase the risk of T2DM complications, such as macroalbuminuria, end-stage renal disease and cardio renal mortality (ischaemic heart disease and diabetic nephropathy combined), by 2–3 times.\textsuperscript{18} Conversely, T2DM also increases the risk of periodontal disease by 2–3 times, with a clear link between the degree of hyperglycaemia, and the onset, extent and severity of periodontal disease.\textsuperscript{22} As such, periodontal disease has been reported as the 6th complication of T2DM, apart from the 5 known systemic complications, namely retinopathy, neuropathy, nephropathy, cardiovascular disease and peripheral vascular disease.\textsuperscript{23}

Findings of mechanistic studies indicate that T2DM leads to a hyperinflammatory response to periodontal microbiota, and impairs resolution of inflammation and repair, which results in accelerated periodontal tissue destruction.\textsuperscript{24} On the other hand, the effect of periodontal disease on T2DM can be partially explained by a corresponding increase in systemic pro-inflammatory mediators, which potentially exacerbates insulin resistance.\textsuperscript{22}

Recent clinical trials in T2DM patients have shown that non-surgical periodontal therapy (for example, scaling and root planing performed by dentists) resulted in a reduction in haemoglobin A1c (HbA1c), ranging from 0.5\%\textsuperscript{26} to 1.5\%\textsuperscript{27} at 3 months—a clinical impact equivalent to adding a second drug to the pharmacological regime for diabetes.\textsuperscript{28} Periodontal therapy has also reduced serum inflammatory markers, such as high-sensitivity C-reactive protein,\textsuperscript{26,29,30} granulocyte colony-stimulating factor\textsuperscript{31} and interleukin-6/tumour necrosis factor α (TNF-α),\textsuperscript{26} at 3–6 months post-intervention. It is likely that periodontal therapy improves glycaemic

![Fig. 1. Stages of periodontal disease and clinical signs.](image-url)
control, through reduced levels of serum inflammatory markers and/or improved insulin resistance. The updated evidence from these studies reaffirms that routine in-clinic periodontal treatment procedures have a direct positive clinical effect on disease prognosis of T2DM patients.

Collectively, recent and consistent findings from clinical studies indicate a strong association of periodontal disease with T2DM. Possible confounders, such as sociodemographic factors and oral health behaviours, are commonly controlled in most of these reported studies. Mechanistic studies have shed light on a biological plausibility for the link between periodontal disease and T2DM, and the number of long-term (>5 years) cohort studies is increasing. This supports a temporal relationship, along with a dose-response relationship between increasing severity of periodontal disease and risk of T2DM (online Supplementary Materials, Table S1). The link between periodontal disease and T2DM is also supported by clinical trials showing positive diabetic management after periodontal therapies (online Supplementary Table S1).

Periodontal disease and cardiovascular diseases

Periodontal disease has also been identified as an independent risk factor for the development of atherosclerotic vascular disease, with systemic inflammation suggested as a potential underlying mechanism. Pooled analysis of observational studies showed a 34% increased risk of developing cardiovascular disease in individuals with existing periodontal disease. Recent large-scale cohort studies with >10 years of follow-ups in American and Korean populations reported a 2-fold increased risk of stroke (for both cardioembolic and thrombotic subtypes), and increased risk of myocardial infarction and stroke in those with severe periodontal disease, respectively. A recent meta-analysis has associated tooth loss, which is a common sequela of severe periodontal disease, with increased risk of cardiovascular disease and stroke, along with a dose-response relationship (i.e. every 2 subsequent teeth lost was associated with a 3% higher risk of coronary heart disease and a 3% higher risk of stroke). Low-grade systemic inflammation and redox imbalance are plausible mechanisms for links between periodontal disease with hypertension and/or endothelial dysfunction, with the effect mediated by inflammatory markers.

Clinical trials have shown that professional dental prophylaxis and intensive periodontal therapy resulted in short-term improvement in surrogate markers of cardiovascular diseases, such as improvement in endothelial function by 1.7% and 3.7%, and reduction in blood pressure by 7mmHg and 12mmHg. More importantly, periodontal therapy has resulted in 10–14% reduction in the incidence of major cardiovascular events across over 10 years of follow-up period. Encouraging patients to maintain good personal oral hygiene may be beneficial for general health, as individuals who never/rarely brushed their teeth had 70% higher incidence of coronary heart disease, compared to those who brushed frequently (twice a day). Recently, frequent toothbrushing (≥3 times a day) was associated with 10% and 12% lower risk of atrial fibrillation and heart failure, respectively, in a nationwide cohort study in a Korean population.

In summary, evidence from long-term (>5 years) cohort studies supports a temporal relationship between periodontal disease and development of cardiovascular disease (online Supplementary Table S2). Routine periodontal therapy has been shown to improve cardiovascular disease markers, such as increased endothelial function and decreased blood pressure (online Supplementary Table S2). Since T2DM is also an independent predictor of cerebrovascular/coronary diseases, timely periodontal therapy is likely to have multiple systemic benefits in such comorbid conditions. As for possible mechanisms, it has been indicated that periodontal therapy reduces the risk of atherogenic vascular disease by improving the plasma levels of inflammatory (C-reactive protein and TNF-α) and metabolic markers (triglycerides and HbA1c), and endothelial function.

Periodontal disease and adverse pregnancy outcomes

Epidemiological studies predominantly support a positive association between maternal periodontal disease and adverse pregnancy outcomes. Pregnant women with periodontal disease have exhibited a 2-fold risk of preterm birth, preeclampsia and low-birth-weight babies. Periodontal disease is posited to affect maternal and fetal immune responses systemically, leading to premature labour, while oral bacteria may translocate directly into the pregnant uterus, causing localized inflammation and adverse pregnancy outcome.

Although successful treatment of periodontal disease has improved pregnancy outcomes, such as through reduced risk of preterm birth, the evidence still remains inconclusive as no effect was seen in some trials. The type of periodontal treatment and its timing during pregnancy may be critical in its effect on individual pregnancy outcomes. Collectively, current evidence supports that periodontal disease, especially...
severe forms during pregnancy, is an independent risk factor for adverse pregnancy outcomes, with timely periodontal therapy potentially useful in mitigating its deleterious effect. Additional data from future observational studies (with a temporal study design) and/or clinical trials (showing positive treatment benefits) are needed to investigate potential causal relationship.

**Periodontal condition and respiratory diseases**

Periodontal disease has been reported as an independent risk factor for chronic obstructive pulmonary disease (COPD), with a 2-fold increased risk of COPD in individuals with periodontal disease, after controlling for common confounders, such as smoking. A recent meta-analysis of observational studies has shown a 50% increased risk of lung cancer among individuals with periodontal disease and an almost 2-fold increased risk in edentulous individuals. Current evidence has also linked periodontal disease with asthma, with significant differences in periodontal parameters between asthmatic and non-asthmatic patients.

Poor oral hygiene may also increase the risk of bacterial pneumonia and mortality. Higher risk of aspiration pneumonia, and infectious and cardiovascular complications were observed among stroke survivors with poor oral hygiene following hospital discharge. For edentulous individuals, good tongue hygiene has been shown to substantially lower the risk of developing aspiration pneumonia by almost 88%. It seems imperative to incorporate oral hygiene care as part of post-stroke rehabilitation to prevent complications that could impair recovery and/or longevity.

**Periodontal disease and other systemic conditions**

Emerging evidence suggests that periodontal disease may be linked to various other systemic conditions. Recent meta-analyses of observational studies demonstrated increased risk of Alzheimer’s disease, chronic kidney disease, rheumatoid arthritis, and liver cirrhosis, in individuals with periodontal disease, especially those with severe periodontitis.

**Clinical and policy implications**

Even though oral diseases are highly prevalent, affecting 3.5 billion people worldwide, they are largely neglected and rarely viewed as a part of mainstream healthcare practice and policy. The emerging evidence clearly indicates that pathologic conditions in the mouth have a much greater systemic impact than many would usually expect. This rapidly accumulating and compelling evidence has several clinical and policy implications.

Awareness and knowledge of oral health among healthcare practitioners is observed to be inadequate. Informing practitioners about the general health impact of oral infections may assist them to develop a more holistic plan for clinical management. Such awareness about oral-systemic links would also encourage practitioners to proactively engage and educate patients to be more aware of the common signs of periodontal disease (e.g. red/swollen gums, loose teeth, etc.) and seek dental care in a timely manner.

Inter-professional collaboration and partnership are advocated for the co-management of medical and dental conditions that are linked, but currently managed by separate groups of healthcare professionals. Closer communication, information exchange and decision support will contribute to better quality of care and optimised healthcare outcomes. Co-management of diabetes and periodontal disease, through a multidisciplinary approach, has been advocated by the International Diabetes Federation and the European Federation of Periodontology in their recent consensus report and guidelines. Periodontal screening and non-surgical periodontal therapy have also been recommended as part of antenatal care, at least before the second trimester of pregnancy, to minimise the potential deleterious effects of active periodontal disease on neonatal/perinatal outcomes.

Finally, policy initiatives will be the keys to success in order to catalyse positive changes in practice. There is a need to develop referral channels for patients suffering from comorbid dental and medical conditions, to enable and support care integration and care transition. Singapore has made a significant move towards integrated care by colocating dental services with medical services in the polyclinics. With this, dental prophylaxis and periodontal therapy can be integrated into primary care. Strategies to incentivise holistic care, such as through subsidies for patients with complex medical needs and prioritisation of inter-professional appointments, can be explored. Evidence of oral-systemic links can be introduced to the undergraduate curriculum, postgraduate courses and continuing professional education programmes to better equip future and current practitioners for integrated patient care.

**CONCLUSION**

The links between oral conditions and general health are multifaceted and complex. While evidence linking periodontal disease with a variety of systemic conditions continues to emerge, recent findings are pointing towards
a robust relationship. Current understanding indicates that successful control of periodontal infections and dental prophylaxis improves diabetic, cardiovascular and pregnancy outcomes. The links between oral infections and major systemic diseases will likely encourage stakeholders (research, academic and clinical communities, as well as governmental organisations and civil society) to make a concerted effort towards developing a sustainable, patient-centric model for managing comorbid dental and medical conditions.

REFERENCES

1. Mayo CH. Mouth infection as a source of systemic disease. JAMA 1914;LXIII:2025-6.
2. Li X, Kolltveit KM, Tronstad L, et al. Systemic diseases caused by oral infection. Clin Microbiol Rev 2000;13:547-58.
3. Peng X, Cheng L, You Y, et al. Oral microbiota in human systemic diseases. Int J Oral Sci 2022;14:14.
4. Clark D, Kotronia E, Ramsay SE. Frailty, aging, and periodontal disease: Basic biologic considerations. Periodontol 2000 2021; 87:143-56.
5. Kapila YL. Oral health’s inextricable connection to systemic health: Special populations bring to bear multimodal relationships and factors connecting periodontal disease to systemic diseases and conditions. Periodontol 2000 2020;87:11-6.
6. Hajishengallis G, Chavakis T. Local and systemic mechanisms linking periodontal disease and inflammatory comorbidities. Nat Rev Immunol 2021;21:426-40.
7. Stöhr J, Barabesko J, Neuenschwander M, et al. Bidirectional association between periodontal disease and diabetes mellitus: a systematic review and meta-analysis of cohort studies. Sci Rep 2021;11:13686.
8. Dietrich T, Sharma P, Walter C, et al. The epidemiological evidence behind the association between periodontitis and incident atherosclerotic cardiovascular disease. J Clin Periodontol 2013;40(Suppl 14):S70-84.
9. Komine-Aizawa S, Aizawa S, Hayakawa S. Periodontal diseases and adverse pregnancy outcomes. J Obstet Gynaecol Res 2019;45:5-12.
10. Wong LY, Toh MP, Tham LW. Projection of prediabetes and diabetes population size in Singapore using a dynamic Markov model. J Diabetes 2017;9:65-75.
11. Tan KW, Dickens BSL, Cook AR. Projected burden of type 2 diabetes mellitus-related complications in Singapore until 2050: a Bayesian evidence synthesis. BMJ Open Diabetes Res Care 2020;8:e000928.
12. Könönen E, Gursoy M, Gursoy UK. Periodontitis: A Multifacetted Disease of Tooth-Supporting Tissues. J Clin Med 2019;8:1135.
13. Konkel JE, O’Boyle C, Krishnan S. Distal Consequences of Oral Inflammation. Front Immunol 2019;10:1403.
14. Kassebaum NJ, Bernabe E, Dahiya M, et al. Global burden of severe periodontitis in 1990-2010: a systematic review and meta-regression. J Dent Res 2014;93:1045-53.
15. Chen MX, Zhong YJ, Dong QQ, et al. Global, regional, and national burden of severe periodontitis, 1990–2019: An analysis of the Global Burden of Disease Study 2019. J Clin Periodontol 2021;48:1165-88.
16. Society of Periodontology, Singapore. Do I have gum disease? https://www.perio.org.sg/do-i-have-gum-disease. Accessed 19 September 2022.
17. Chiu CT, Malhotra R, Tan SM, et al. Dental health status of community-dwelling older Singaporeans: findings from a nationally representative survey. Gerodontology 2017;34:57-67.
18. Preshaw PM, Alba AL, Herrera D, et al. Periodontitis and diabetes: a two-way relationship. Diabetologia 2012;55:21-31.
19. Graziani F, Gennai S, Solini A, et al. A systematic review and meta-analysis of epidemiologic observational evidence on the effect of periodontitis on diabetes An update of the EFP-AAP review. J Clin Periodontol 2018;45:167-87.
20. Lin SY, Lin CL, Liu JH, et al. Association between periodontitis needing surgical treatment and subsequent diabetes risk: a population-based cohort study. J Periodontol 2014;85:779-86.
21. Myllymäki V, Saxlin T, Knuttila M, et al. Association between periodontal condition and the development of type 2 diabetes mellitus-Results from a 15-year follow-up study. J Clin Periodontol 2018;45:1276-86.
22. Mealey BL, Ocampo GL. Diabetes mellitus and periodontal disease. Periodontol 2000 2007;44:127-53.
23. Loe H. Periodontal disease. The sixth complication of diabetes mellitus. Diabetes Care 1993;16:329-34.
24. Salvi GE, Beck JD, Offenbacher S. PGE2, IL-1 beta, and TNF-alpha responses in diabetics as modifiers of periodontal disease expression. Ann Periodontol 1998;3:40-50.
25. Demmer RT, Squillaro A, Papapanou PN, et al. Periodontal infection, systemic inflammation, and insulin resistance: results from the continuous National Health and Nutrition Examination Survey (NHANES) 1999-2004. Diabetes Care 2012;35:2235-42.
26. Sun WL, Chen LL, Zhang SZ, et al. Inflammatory cytokines, adiponectin, insulin resistance and metabolic control after periodontal intervention in patients with type 2 diabetes and chronic periodontitis. Intern Med 2011;50:1569-74.
27. O’Connell PA, Taba M, Nomizo A, et al. Effects of periodontal therapy on glycemic control and inflammatory markers. J Periodontol 2008;79:774-83.
28. Dörfer C, Benz C, Aida J, et al. The relationship of oral health with general health and NCDs: a brief review. Int Dent J 2017;67(Suppl 2):14-8.
29. Chen L, Luo G, Xian D, et al. Effects of non-surgical periodontal treatment on clinical response, serum inflammatory parameters, and metabolic control in patients with type 2 diabetes: a randomized study. J Periodontol 2012;83:435-43.
30. Raman RP, Taiyeb-Ali TB, Chan SP, et al. Effect of nonsurgical periodontal therapy verses oral hygiene instructions on type 2 diabetes subjects with chronic periodontitis: a randomised controlled trial. BMC Oral Health 2014;14:79.
31. O’Connell PAA, Taba M Jr, Nomizo A, et al. Effects of Periodontal Therapy on Glycemic Control and Inflammatory Markers. J Periodontol 2008;79:774-83.
32. Iwamoto Y, Nishimura F, Nakagawa M, 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.
33. Baesa M, Morales A, Cisterna C, et al. Effect of periodontal treatment in patients with periodontitis and diabetes: systematic review and meta-analysis. J Appl Oral Sci 2020;28:e20190248.
34. Lockhart PB, Bolger AF, Papapanou PN, et al. Periodontal disease and atherosclerotic vascular disease: does the evidence support an independent association?: a scientific statement from the American Heart Association. Circulation 2012;125:2520-44.
35. Blaizot A, Vergnes JN, Nuwwarah S, et al. Periodontal diseases and cardiovascular events: meta-analysis of observational studies. Int Dent J 2009;59:197-209.

36. Sen S, Giamberardino LD, Moss K, et al. Periodontal Disease, Regular Dental Care Use, and Incident Ischemic Stroke. Stroke 2018;49:355-62.

37. Cho HJ, Shin MS, Song Y, et al. Severe Periodontal Disease Increases Acute Myocardial Infarction and Stroke: A 10-Year Retrospective Follow-up Study. J Dent Res 2021;100:706-13.

38. Cheng F, Zhang M, Wang Q, et al. Tooth loss and risk of cardiovascular disease and stroke: A dose-response meta analysis of prospective cohort studies. PloS One 2018;13:e0194563.

39. Del Pinto R, Pietropaoli D, Munoz-Aguilera E, et al. Periodontitis and Hypertension: Is the Association Causal? High Blood Press Cardiovasc Prev 2020;27:281-9.

40. Pietropaoli D, Del Pinto R, Ferri C, et al. Association between periodontal inflammation and hypertension using periodontal inflamed surface area and bleeding on probing. J Clin Periodontol 2020;47:160-72.

41. Czesnikiewicz-Guzik M, Osmenda G, Siedlinski M, et al. Causal association between periodontitis and hypertension: evidence from Mendelian randomization and a randomized controlled trial of non-surgical periodontal therapy. Eur Heart J 2019;40:3459-70.

42. Seinost G, Wimmer G, Skerget M, et al. Periodontal treatment improves endothelial dysfunction in patients with severe periodontitis. Am Heart J 2005;149:1050-4.

43. Hada DS, Garg S, Ramteke GB, et al. Effect of Non-Surgical Periodontal Treatment on Clinical and Biochemical Risk Markers of Cardiovascular Disease: A Randomized Trial. J Periodontol 2015;86:1201-11.

44. Zhou QB, Xia WH, Ren J, et al. Effect of Intensive Periodontal Therapy on Blood Pressure and Endothelial Microparticles in Patients With Prehypertension and Periodontitis: A Randomized Controlled Trial. J Periodontol 2017;88:711-22.

45. Holmlund A, Lampa E, Lind L. Poor Response to Periodontal Treatment May Predict Future Cardiovascular Disease. J Dent Res 2017;96:768-73.

46. Lee YL, Hu HY, Chou P, et al. Dental prophylaxis decreases the risk of acute myocardial infarction: a nationwide population-based study in Taiwan. Clin Interv Aging 2015;10:175-82.

47. Park SY, Kim SH, Kang SH, et al. Improved oral hygiene care attenuates the cardiovascular risk of oral health: a population-based study from Korea. Eur Heart J 2019;40:1138-45.

48. de Oliveira C, Watt R, Hamer M. Toothbrushing, inflammation, and risk of cardiovascular disease: results from Scottish Health Survey. BMJ 2010;340:c2451.

49. Chang Y, Woo HG, Park J, et al. Improved oral hygiene care is associated with decreased risk of occurrence for atrial fibrillation and heart failure: A nationwide population-based cohort study. Eur J Prev Cardiol 2020;27:1835-45.

50. The EZ, Ng MY, Ng GJ, et al. Long-term outcomes of ischaemic stroke patients with diabetes in a multi-ethnic cohort in Singapore. Ann Acad Med Singap 2021;50:16-25.

51. Teeuw WJ, Slot DE, Susanto H, et al. Treatment of periodontitis improves the atherosclerotic profile: a systematic review and meta-analysis. J Clin Periodontol 2014;41:70-9.

52. Manrique-Corredor EJ, Orozco-Beltran D, Lopez-Pineda A, et al. Maternal periodontitis and preterm birth: Systematic review and meta-analysis. Community Dent Oral Epidemiol 2019;47:243-51.

53. Wei BJ, Chen YJ, Yu L, et al. Periodontal disease and risk of pre eclampsia: a meta-analysis of observational studies. PloS One 2013;8:e70901.

54. Zhang Y, Feng W, Li J, et al. Periodontal Disease and Adverse Neonatal Outcomes: A Systematic Review and Meta-Analysis. Front Pediatr 2022;10:799740.

55. Han YW. Oral health and adverse pregnancy outcomes - what's next? J Dent Res 2011;90:289-93.

56. Jeffcoat M, Parry S, Sammel M, et al. Periodontal infection and preterm birth: successful periodontal therapy reduces the risk of preterm birth. BJOG 2011;118:250-6.

57. Reddy BV, Tanneur S, Chava VK. The effect of phase-I periodontal therapy on pregnancy outcome in chronic periodontitis patients. J Obset Gynaecol 2014;34:29-32.

58. Taranum F, Faizuddin M. Effect of periodontal therapy on pregnancy outcome in women affected by periodontitis. J Periodontol 2007;78:2095-103.

59. Michalowicz BS, Hodges JS, DiAngelis AJ, et al. Treatment of periodontal disease and the risk of preterm birth. N Engl J Med 2006;355:1885-94.

60. Caneiro-Quejia L, López-Carral J, Martin-Lancharro P, et al. Non-Surgical Treatment of Periodontal Disease in a Pregnant Caucasian Women Population: Adverse Pregnancy Outcomes of a Randomized Clinical Trial. Int J Environ Res Public Health 2019;16:3638.

61. Pirie M, Linden G, Irwin C. Intrapregnancy non-surgical periodontal treatment and pregnancy outcome: a randomized controlled trial. J Periodontol 2013;84:1391-400.

62. Le QA, Eslick GD, Coulton KM, et al. Differential impact of periodontal treatment strategies during pregnancy on perinatal outcomes: a systematic review and meta-analysis. J Evid Based Dent Pract 2022;22:101666.

63. Zeng XT, Tu ML, Liu DY, et al. Periodontal disease and risk of chronic obstructive pulmonary disease: a meta-analysis of observational studies. PloS One 2012;7:e46508.

64. Wang J, Yang X, Zou X, et al. Relationship between periodontal disease and lung cancer: A systematic review and meta-analysis. J Periodontol Res 2020;55:581-93.

65. Moraschini V, Calansas-Maia JA, Calansas-Maia MD. Association between asthma and periodontal disease: A systematic review and meta-analysis. J Periodontol 2018;89:440-55.

66. Kwok C, McIntyre A, Janzen S, et al. Oral care post stroke: a scoping review. J Oral Rehabil 2015;42:65-75.

67. Lam OL, McMillan AS, Li LS, et al. Oral health and post-discharge complications in stroke survivors. J Oral Rehabil 2016;43:238-40.

68. Abe S, Ishihara K, Adachi M, et al. Tongue-coating as risk indicator for aspiration pneumonia in edentate elderly. Arch Gerontol Geriatr 2008;47:267-75.

69. Deschamps-Lenhardt S, Martin-Cabezas R, Hannedouche T, et al. Association between periodontitis and chronic kidney disease: Systematic review and meta-analysis. Oral Dis 2019;25:385-402.

70. Qiao Y, Wang Z, Li Y, et al. Rheumatoid arthritis risk in periodontitis patients: A systematic review and meta-analysis. Joint Bone Spine 2020;87:556-64.

71. Chen Y, Yang YC, Zhu BL, et al. Association between periodontal disease, tooth loss and liver diseases risk. J Clin Periodontol 2020;47:1053-63.

72. Watt RG, Daly B, Allison P, et al. Ending the neglect of global oral health: time for radical action. Lancet 2019;394:261-72.
73. Peck CC. Putting the Mouth into Health: The Importance of Oral Health for General Health. In: Sasaki K, Suzuki O, Takahashi N (Eds). Interface Oral Health Science. Singapore: Springer; 2016.

74. Kapila YL. Oral health’s inextricable connection to systemic health: Special populations bring to bear multimodal relationships and factors connecting periodontal disease to systemic diseases and conditions. Periodontology 2020 2021;87:11-6.

75. Grocock R, Holden B, Robertson C. The missing piece of the body? Oral health knowledge and confidence of doctors. Br Dent J 2019;226:427-31.

76. Aggelidou Galazi A, Siskou O, Karagkouni I, et al. Investigating physicians’ and patients’ oral health knowledge: a field needed interdisciplinary policy making approach. Int J Health Promot Educ 2019;57:343-54.

77. Thomson A, Dickenson AJ, Ross-Russell M. Integrated care: a new model for dental education. Br Dent J 2021;231:187-90.

78. Lobbezoo F, Aarab G. The global oral health workforce. Lancet 2021;398:2245.

79. Sanz M, Ceriello A, Buysschaert M, et al. Scientific evidence on the links between periodontal diseases and diabetes: Consensus report and guidelines of the joint workshop on periodontal diseases and diabetes by the International Diabetes Federation and the European Federation of Periodontology. Diabetes Res Clin Pract 2018;137:231-41.

80. Govindasamy R, Periyasamy S, Narayanan M, et al. The influence of nonsurgical periodontal therapy on the occurrence of adverse pregnancy outcomes: A systematic review of the current evidence. J Indian Soc Periodontol 2020;24:7-14.

81. Harnagea H, Lamothe L, Couturier Y, et al. From theoretical concepts to policies and applied programmes: the landscape of integration of oral health in primary care. BMC Oral Health 2018;18:23.

82. Demmer RT, Jacobs DR Jr, Desvarieux M. Periodontal disease and incident type 2 diabetes: results from the First National Health and Nutrition Examination Survey and its epidemiologic follow-up study. Diabetes Care 2008;31:1373-9.

83. Miyawaki A, Toyokawa S, Inoue K, et al. Self-Reported Periodontitis and Incident Type 2 Diabetes among Male Workers from a 5-Year Follow-Up to MY Health Up Study. PLoS One 2016;11:e0153464.

84. Winning L, Patterson CC, Neville CE, et al. Periodontitis and incident type 2 diabetes: a prospective cohort study. J Clin Periodontol 2017;44:266-74.

85. Morita I, Inagaki K, Nakamura F, et al. Relationship between periodontal status and levels of glycated hemoglobin. J Dent Res 2012;91:161-6.

86. Chiu SY, Lai H, Yen AM, et al. Temporal sequence of the bidirectional relationship between hyperglycemia and periodontal disease: a community-based study of 5,855 Taiwanese aged 35–44 years (KCIS No. 32). Acta Diabetol 2015;52:123-31.

87. Rodrigues DC, Taha M Jr, Novaes AB Jr, et al. Effect of Non-Surgical Periodontal Therapy on Glycemic Control in Patients with Type 2 Diabetes Mellitus. J Periodontol 2003;74:1361-7.

88. Koromantzos PA, Makrilakis K, Deka X, et al. A randomized, controlled trial on the effect of non-surgical periodontal therapy in patients with type 2 diabetes. Part I: effect on periodontal status and glycemic control. J Clin Periodontol 2011;38:142-7.

89. Moeintaghavi A, Arab HR, Bozorgnia Y, et al. Non-surgical periodontal therapy affects metabolic control in diabetics: a randomized controlled clinical trial. Aust Dent J 2012;57:31-7.

90. Tsobgny-Tsague NF, Lontchi-Yimagou E, Nana ARN, et al. Effects of nonsurgical periodontal treatment on glycated haemoglobin on type 2 diabetes patients (PARODIA 1 study): a randomized controlled trial in a sub-Saharan Africa population. BMC Oral Health 2018;18:28.

91. El-Makaky Y, Shalaby HK. The effects of non-surgical periodontal therapy on glycemic control in diabetic patients: A randomized controlled trial. Oral Dis 2020;26:822-9.

92. Dorn JM, Genco RJ, Grossi SG, et al. Periodontal disease and recurrent cardiovascular events in survivors of myocardial infarction (MI): the Western New York Acute MI Study. J Periodontol 2010;81:502-11.

93. Xu F, Lu B. Prospective association of periodontal disease with cardiovascular and all-cause mortality: NHANES III follow-up study. Atherosclerosis 2011;218:536-42.

94. Yu YH, Chassman DI, Buring JE, et al. Cardiovascular risks associated with incident and prevalent periodontal disease. J Clin Periodontol 2015;42:21-8.

95. Bengtsson VW, Persson GR, Berglund JS, et al. Periodontitis related to cardiovascular events and mortality: a long-time longitudinal study. Clin Oral Investig 2021;25:4085-95.

96. Cho JJ, Shin MS, Song Y, et al. Severe Periodontal Disease Increases Acute Myocardial Infarction and Stroke: A 10-Year Retrospective Follow-up study. J Dent Res 2021;100:706-13.

97. Tonetti MS, D’Auito F, Nibali L, et al. Treatment of periodontitis and endothelial function. N Engl J Med 2007;356:911-20.