

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.

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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.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.^{2,3}

In particular, periodontal disease, a highly prevalent chronic inflammatory disease of tooth-supporting structures,⁴ has been linked to a wide range of common medical conditions.^{5,6} Scientific evidence suggests periodontal disease to be associated with type 2 diabetes mellitus (T2DM),⁷ cardiovascular disease⁸ and adverse pregnancy outcomes,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,

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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

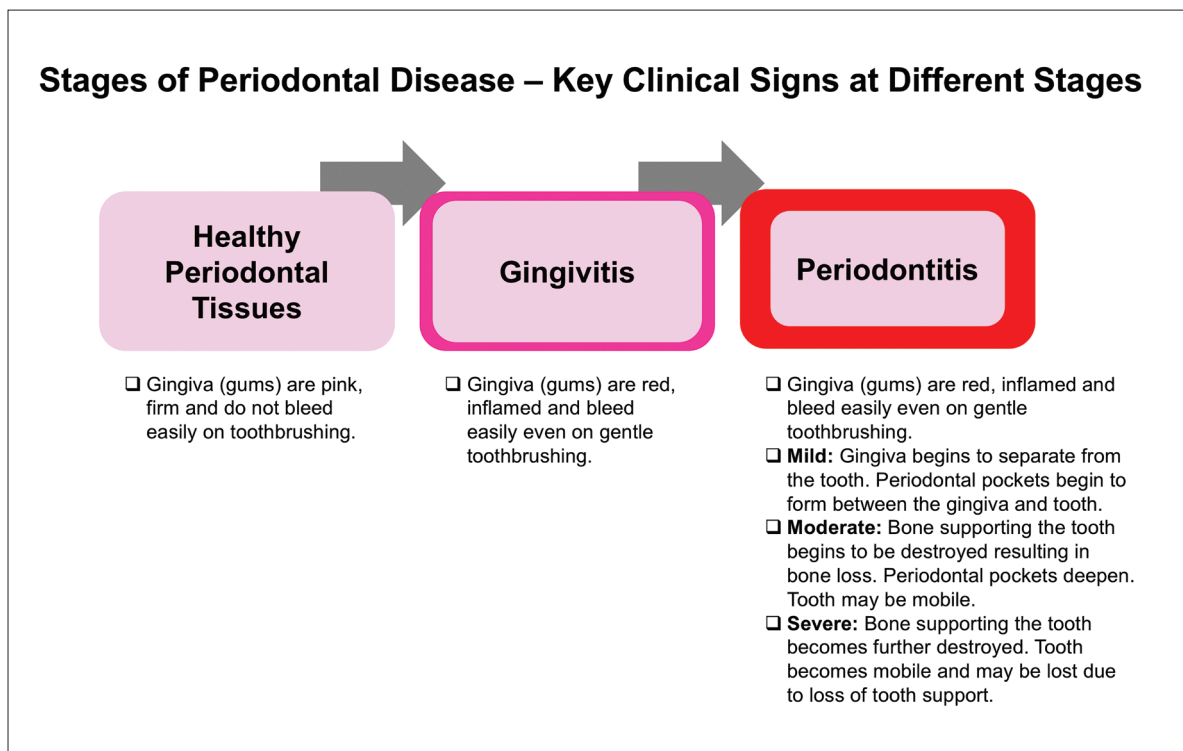


Fig. 1. Stages of periodontal disease and clinical signs.

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.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.¹⁸ Individuals with periodontal disease exhibited poorer glycaemic control and have 19–33% higher risk of developing diabetes,¹⁹ with the highest incidence reported in those with severe periodontal disease.^{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 cardiorenal mortality (ischaemic heart disease and diabetic nephropathy combined), by 2–3 times.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.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.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.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.²⁵

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%²⁶ to 1.5%²⁷ at 3 months—a clinical impact equivalent to adding a second drug to the pharmacological regime for diabetes.²⁸ Periodontal therapy has also reduced serum inflammatory markers, such as high-sensitivity C-reactive protein,^{26,29,30} granulocyte colony-stimulating factor³¹ and interleukin-6/tumour necrosis factor α (TNF- α),²⁶ at 3–6 months post-intervention. It is likely that periodontal therapy improves glycaemic

control, through reduced levels of serum inflammatory markers and/or improved insulin resistance.³² 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.³³

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.^{8,34} Pooled analysis of observational studies showed a 34% increased risk of developing cardiovascular disease in individuals with existing periodontal disease.³⁵ 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),³⁶ and increased risk of myocardial infarction and stroke in those with severe periodontal disease, respectively.³⁷ 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).³⁸ Low-grade systemic inflammation and redox imbalance are plausible mechanisms for links between periodontal disease with hypertension and/or endothelial dysfunction,³⁹ with the effect mediated by inflammatory markers.⁴⁰

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%⁴¹ and 3.7%,⁴² and reduction in blood pressure by 7mmHg^{35,43} and 12mmHg.⁴⁴ 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.^{45–47} 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).⁴⁸ 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.⁴⁹

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,⁵⁰ 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.⁵¹

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,⁵² preeclampsia⁵³ and low-birth-weight babies.⁵⁴ 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 localised inflammation and adverse pregnancy outcome.⁵⁵

Although successful treatment of periodontal disease has improved pregnancy outcomes, such as through reduced risk of preterm birth,^{56–58} the evidence still remains inconclusive as no effect was seen in some trials.^{59–61} The type of periodontal treatment and its timing during pregnancy may be critical in its effect on individual pregnancy outcomes.⁶² 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.⁶³ 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.⁶⁴ Current evidence has also linked periodontal disease with asthma, with significant differences in periodontal parameters between asthmatic and non-asthmatic patients.⁶⁵

Poor oral hygiene may also increase the risk of bacterial pneumonia and mortality. Higher risk of aspiration pneumonia,⁶⁶ and infectious and cardiovascular complications were observed among stroke survivors with poor oral hygiene following hospital discharge.⁶⁷ For edentulous individuals, good tongue hygiene has been shown to substantially lower the risk of developing aspiration pneumonia by almost 88%.⁶⁸ 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,⁶⁹ chronic kidney disease,⁶⁹ rheumatoid arthritis⁷⁰ and liver cirrhosis,⁷¹ 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.⁷² The emerging evidence clearly indicates that pathologic conditions in the mouth have a much greater systemic impact than many would usually expect.^{73,74} 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.^{75,76} 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.^{77,78} 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.⁷⁹ 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.⁸⁰

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.⁸¹ 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.⁷⁷

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.

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