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CLINICAL PERSPECTIVES

Oral health and cardiometabolic disease: understanding the relationship

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Abstract

Examination of the oral cavity can identify clinical signs indicative of underlying systemic disease. Key features to examine include the general appearance and number of the teeth, signs of inflammation of the mucosa or gingival tissues including bleeding of the gums and redness, swelling or hyperplasia. Additionally, the tongue should be assessed for any ulceration or discolouration and the presence of excessive build-up (coating). Cardiovascular disease and diabetes, together known as cardiometabolic disease have an impact on oral health. Similarly, oral health conditions, such as gum disease (periodontitis) and dryness of the mouth (xerostomia), are associated with an increased risk for both cardiovascular disease and type 2 diabetes mellitus. The aim of this narrative review is to outline both the impact of periodontitis and xerostomia on cardiometabolic disease and the impact of cardiometabolic health on these oral health conditions. Key features of periodontitis and xerostomia will be provided along with a brief discussion of current concepts in early prevention and management of these oral health conditions. The biological mechanisms linking cardiometabolic disease and periodontitis will be outlined and the evidence supporting the association between cardiometabolic disease and oral health conditions will be presented together with an identification of areas where further research is indicated. Last, guidance for general practitioners to assess and support early diagnosis and management of oral health conditions by raising awareness of the relationship between oral health and cardiometabolic disease, providing simple oral health advice and referring to a dental practitioner will be presented.

Introduction

Manifestations of underlying systemic disease are often reflected in the oral cavity and poor oral health can serve as an indicator of overall health. The main oral health conditions are caries (tooth decay), periodontal diseases, tooth loss and oral cancers. Untreated, these conditions can result in pain, discomfort, reduced quality of life, productivity and in some cases death. The major non-communicable diseases, cardiovascular disease (CVD), stroke and diabetes, together referred to as cardiometabolic disease, can impact on an individual's oral health, and importantly, the oral health can also impact on the pathophysiology of cardiometabolic disease.

Periodontitis (gum disease) is an inflammatory disease of the soft and hard tissues supporting the teeth that is associated with cardiometabolic disease.[1] A dysregulated and chronic inflammatory response characterises periodontitis, which is triggered by a persisting subgingival biofilm.[1] The chronic localised inflammation results in the loss of supporting bone and connective tissue around the teeth, leading to tooth mobility, tooth movement and, untreated, leads to tooth loss.[2] The tissue destruction is mediated partly by oral bacteria; however, 80% of the destruction is mediated by the host's immunological response.[1] In 2017–2018, the prevalence of periodontitis in Australia ranged from 30% in the total population,

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increasing with age to 50.1% in those aged 55–74 years, and to 69.3% in those over the age of 75 years.[3] Lower socioeconomic groups are disproportionately affected.[3] This picture is similar globally, where the prevalence of periodontitis increases with age, is higher in males and peaks between the 5th and 7th decades of life, more severely affecting individuals of lower socioeconomic status.[4] The risk factors for periodontitis are poor oral hygiene and also include risk factors known for cardiometabolic disease, including tobacco smoking, obesity, poor nutrition and physical inactivity.[5] Of concern is the rising incidence of periodontitis in Australia, which increased by 9% between 2004/2006 and 2017/2018.[3]

Another important oral health condition associated with cardiometabolic disease is dry mouth syndrome (xerostomia), which is defined as the subjective experience of a dry mouth. Interestingly, not all patients who report a dry mouth have underlying hyposalivation, measured as an unstimulated salivary flow rate of <0.1 mL/min collected over a 5- to 15-min period, or a stimulated salivary flow rate of <0.7 mL/min collected over 5 min.[6] This suggests that changes in salivary composition and sensory dysfunction could contribute to the experience of xerostomia.

This narrative review aims to provide a brief overview of the clinical presentation and management of periodontitis and xerostomia. The review will describe the consequences of poorly managed periodontitis and xerostomia on both the dentition and the impact on cardiometabolic health. The relationships between both periodontitis and xerostomia and cardiometabolic disease will be outlined and the evidence supporting the association between periodontitis and cardiometabolic disease will be presented. Last, guidance for general practitioners to support the maintenance of good oral health will be discussed.

Clinical presentation of periodontal disease

Poor oral hygiene can lead to the build-up of bacterial deposits (plaque) around the teeth that trigger a local inflammatory reaction in the gingival tissues. The tissues appear red, swollen and bleed easily during tooth brushing. This initial inflammatory reaction is termed gingivitis and is the earliest stage of periodontal disease.[1] Gingivitis is reversible by simple self-performed oral hygiene practices. In some individuals, where there is a persistent accumulation of plaque deposits and an increase in pathogenic bacteria, gingivitis might progress to periodontitis, which is a more advanced stage of periodontal disease.[1] This progression occurs not only due to the persistence of plaque or the increase in pathogenic bacteria, but due to the nature of the host response to the bacterial challenge.[1] (Fig. 1). Untreated, periodontitis in most individuals progresses slowly and is generally painless until it becomes quite advanced; however, in approximately 10% of the population, the disease progresses rapidly and can result in tooth loss in young adults.[1] Early symptoms might include gingival bleeding, halitosis and sensitivity of the teeth as bone is lost and the root surfaces become exposed. The irreversible loss of bone and connective tissue results in the creation of a periodontal pocket, which is a gap between the tooth and the bone. The deeper the pocket, the more tissue damage, and the harder it is for the individual to remove bacterial plaque deposits by daily oral hygiene. Importantly, in some cases the inflammation might not be obvious as it can occur deep within the periodontal pocket in the absence of overt clinical inflammation. Furthermore, as the condition is generally painless, the individual might be unaware of the disease process. As the disease progresses, teeth become mobile (loose), move from their original position (tooth migration) and eventually tooth loss might occur making chewing difficult.[2]

Consequences of periodontitis: tooth loss and masticatory dysfunction

A complete dentition consists of 28 teeth (32 teeth if the four wisdom teeth are included). Periodontitis is the leading cause of tooth loss,[2] which in turn can lead to disturbed masticatory function. In order to maintain satisfactory masticatory performance, a functional dentition is required. This is defined as the presence of a minimum of 20 natural teeth, with 9–10 pairs of teeth in contact when the mouth is closed, no loss of front teeth and the retention of the small molar teeth (premolars). In Australia, approximately 10% of the overall population aged 15 years and over do not have a functional dentition and this increases with age to 46.5% in those aged ≥75 years.[3] Factors affecting a functional dentition are residential location (urban/regional), level of education and socioeconomic status.[3]

Masticatory dysfunction has been shown to contribute to low body mass index and undernutrition.[7] The compromised nutrient intake is driven by altered food choices, where individuals with poor masticatory performance select soft, easy-to-chew food, which is often low in fibre, protein and iron.[8] An important part of managing cardiometabolic disease is ensuring a healthy diet, which includes fresh fruits and vegetables, protein and fibre; however, in individuals with masticatory dysfunction, these may be the very foods that are difficult to chew and are therefore avoided. There are no studies that have investigated the impact of a functional dentition on dietary habits in patients with cardiometabolic disease and this is an area that warrants further investigation.

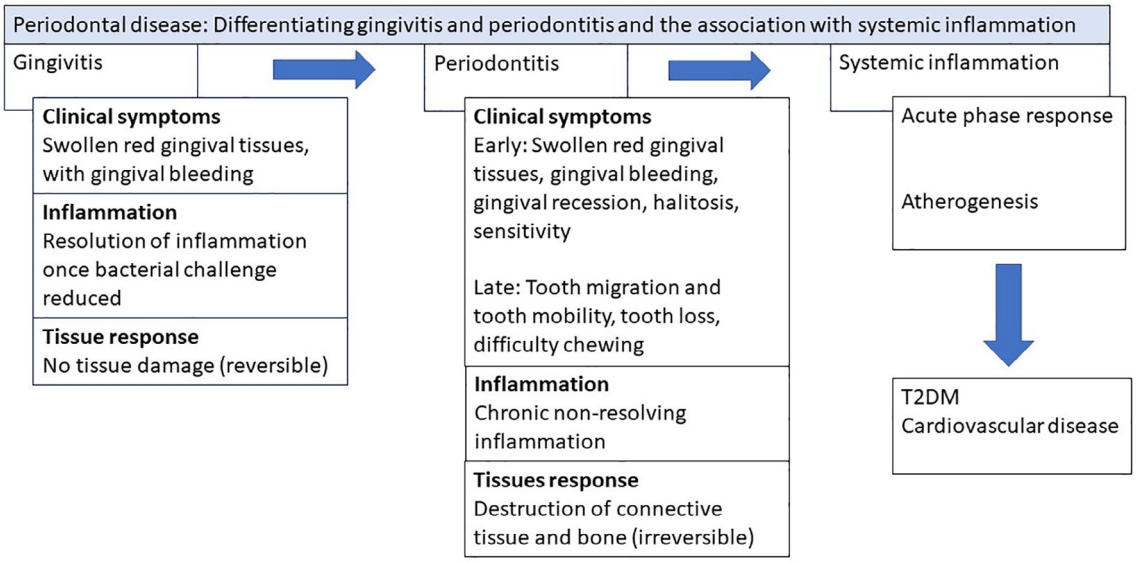

Figure 1 Features of gingivitis and periodontitis and the association with systemic inflammation. Bacterial deposits around the teeth trigger a local inflammatory reaction, the initial inflammatory reaction is termed gingivitis, which is a reversible inflammatory condition. In the presence of persisting bacterial deposits, gingivitis might progress to periodontitis, which is a chronic inflammatory condition that causes destruction of bone and connective tissue around the teeth. Ultimately, this local chronic inflammatory response triggers a systemic inflammatory response and is associated with an increased risk for type 2 diabetes mellitus (T2DM) and cardiovascular disease.

Management of periodontitis

The destruction of connective tissue and bone in periodontitis is irreversible, and the treatment goal is to halt the inflammatory process and prevent further tissue destruction. The treatment of periodontitis is easy and involves a procedure to remove the bacterial deposits adherent to the root surfaces, together with patient education and motivation in oral self-care practices. Periodontitis treatment is followed by a lifelong personalised maintenance programme focussed on behaviour change and regular professional cleaning of the teeth. In some cases, extended surgical treatment is required to expose and clean root surfaces along with antibiotic therapy.

It is important to diagnose early clinical signs of gingivitis (bleeding, swollen gums) as in the early stages the condition is reversible and the inflammation can be resolved by improving self-performed oral hygiene. In contrast, periodontitis is irreversible and requires professional periodontitis treatment.

Bacteraemia and inflammation: biological mechanisms linking cardiometabolic disease and periodontitis

Normal daily activities such as eating, flossing and toothbrushing allow oral bacteria to enter the bloodstream resulting in a bacteraemia.[9] In the presence of periodontitis, these episodes of bacteraemia are more frequent, of longer duration and consist of more virulent bacterial species.[9] Pathogenic oral bacteria associated with periodontitis have been identified in atherothrombotic tissues, and in animal models periodontal pathogens have been shown to induce endothelial dysfunction[10] and accelerate atherosclerosis.[5] This supports a direct effect of periodontal pathogens on atheroma formation suggesting that bacteraemia is a likely mechanism linking periodontitis and CVD. The oral bacteria also trigger a local inflammatory response, resulting in the local production of pro-inflammatory cytokines, such as tumour necrosis factor alpha (TNFα), interleukin-1 beta (IL-1β), interleukin-6 (IL-6), which mediate the tissue damage that characterises the clinical features of periodontitis.[1] The cytokines also enter the bloodstream to induce an acute phase response leading to the release of C-reactive protein, activation of cytokine networks and neutrophils to release oxygen radicals (oxidative stress response), thereby contributing to the development of an underlying state of chronic systemic inflammation.[11] The systemic inflammation increases the risk for CVD and contributes to poor beta cell function and insulin resistance, thereby increasing the risk for type 2 diabetes mellitus (T2DM).[9] (Fig. 1). Periodontal treatment reduces systemic inflammatory markers such as C-reactive protein, and IL-6 and reduces circulating lipids supporting the role of inflammation as a biological

mechanism linking periodontitis with cardiometabolic disease.[5] However, the association between periodontitis and diabetes is bidirectional, in that the increase in adiposity and circulating pro-inflammatory cytokines that occurs in diabetes is also thought to exacerbate the local periodontal response.[9]

Cardiovascular disease and periodontitis

This narrative review identified three meta-analyses of observational studies that analysed the risk of CVD outcomes in individuals with periodontitis.[12–15] The evidence from these studies demonstrates that individuals with periodontitis have a moderate but consistently increased risk of coronary heart disease (CHD),[12,14,15] ischaemic stroke[13,14] and CVD,[14] as summarised in Table 1.

Additionally, a recent systematic review of 40 studies has shown that moderate to severe periodontitis is associated with a 22% increase in the risk of hypertension, while severe periodontitis is associated with a 49% increase in the risk for hypertension.[16]

However, there have been no large randomised controlled trials demonstrating the impact of periodontitis treatment on cardiovascular outcomes. There are several challenges involved in conducting a randomised controlled trial. Periodontitis is slowly progressive and the effect on CVD is small, therefore a large number of participants would need to be reviewed over a long period to observe significant differences in CVD endpoints. Furthermore, establishing an appropriate control group in whom periodontal treatment is withheld over a long observation period is not ethically feasible and was highlighted in a small pilot study.[17] Therefore, a causal relationship between periodontitis and CVD endpoints has not yet been established. The available trial evidence suggests that periodontitis treatment results in a reduction in markers of CVD, including inflammatory markers like C-reactive protein, and circulating lipids.[5,18] More recently, it has been demonstrated that periodontitis treatment reduces the systolic blood pressure in patients with hypertension.[16]

There is currently ongoing discussion whether individuals with CVD have, or do not have, a higher incidence or rate of progression of periodontitis. The observational evidence indicates that individuals with periodontitis have an increased risk for CVD events, and that more severe stages of periodontitis are associated with a higher CVD risk.[5] Importantly, periodontitis treatment has been shown to reduce the systemic inflammatory burden.[5] Therefore, individuals diagnosed with CVD, or related risk factors such as hypertension, and elevated lipid levels, should be encouraged to maintain good oral health, and seek professional assessment and management of their gums, as reducing the oral inflammatory burden is likely to lower their CVD risk.

As previously discussed, tooth loss is considered an endpoint of periodontitis and therefore is an easily accessible marker of periodontitis history in individuals. As a result, tooth loss has been used to investigate the relationship between periodontitis and cardiometabolic disease. A study involving over 4 million Koreans demonstrated a dose-dependent association between the number of missing teeth and the risk for myocardial infarction. Each missing tooth increased the risk for myocardial infarction by 1%, heart failure and ischaemic stroke by 1.5% and all cause death by 2%.[19] Similarly, an Australian study has shown that the number of missing teeth is a positive predictor for CVD-related hospitalisations[20] and a Japanese study has demonstrated that poor glycaemic control is strongly associated with the number of remaining teeth.[21] These findings suggest that the number of missing teeth might be used as a predictive risk factor for cardiometabolic disease outcomes.

Diabetes and periodontitis

The association between T2DM and periodontitis has been shown to be bidirectional. In a recent meta-analysis of 15 prospective cohort studies individuals with diabetes, with poor glycaemic control, had a 24% (95% confidence

Table 1 Summary of meta-analyses on association between periodontal disease and cardiovascular disease

Study	Study types	Outcome measures	RR (95% CI)
Humphrey *et al.*[15]	6 × Cohort studies	CHD	1.24 (1.01–1.51)
Leng *et al.*[12]	18 × Prospective cohort studies	CHD	1.19 (1.13–1.26)
Leira *et al.*[13]	3 × Prospective cohort studies	Ischaemic stroke	2.52 (1.77–3.58)
	5 × Case−control studies	Ischaemic stroke	3.04 (1.10–8.43)
Larvin *et al.*[14]	30 × Prospective and retrospective cohort studies	All CVD	1.20 (1.14–1.26)
		Ischaemic stroke	1.24 (1.12–1.38)
		CHD	1.14 (1.08–1.21)

CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; RR, relative risk.

interval (CI) 13–37%) increase in their risk for developing periodontitis compared with those without diabetes.[22] Similarly, in individuals with periodontitis, the risk for developing diabetes was increased by 26% (95% CI 12–41%) compared with periodontally healthy individuals.[22] More studies are required as this is the first meta-analysis to analyse both directions of this relationship separately. Intervention studies have demonstrated that periodontitis treatment reduces systemic levels of pro-inflammatory cytokines and is associated with reductions in HbA1c levels of 0.27–0.48% after 3–4 months.[22] Long-term outcomes are not available.[23] Importantly, the effect of periodontitis treatment on lowering HbA1c has been noted in patients withT2DM; however, there is insufficient evidence for a similar effect in type 1 diabetes mellitus.[23]

Notably, even in individuals without diabetes, periodontitis is associated with higher HbA1c levels, when compared with individuals with healthy gums. In individuals with T2DM, periodontitis is associated with poor glycaemic control, as measured by HbA1c levels compared to those with T2DM and no periodontitis.[23] Additionally, there is emerging evidence that the presence of periodontitis as a comorbidity impacts on diabetes-related complications, for example, in people with diabetes, the severity of periodontitis correlates with the severity of retinopathy and is associated with an increased risk for retinopathy (odds ratio (OR) 1.2–2.8), increases the risk of renal complications (OR 1.9–8.6), increases the risk for neuropathy (OR 3.2–6.6) and increases cardiovascular complications (OR 1.2–17.7) with a significant increase in overall mortality (OR 2.3–8.5).[24] Further research is required to investigate whether periodontitis treatment reduces the number or severity of diabetes complications.

Based on the available evidence, patients diagnosed with T2DM, or pre-diabetes, should be made aware that their risk for periodontitis is increased and that untreated periodontitis may compromise their glycaemic control and increase their risk for diabetes-related complications.

Cardiometabolic disease and xerostomia

Numerous observational studies report an increased prevalence of xerostomia in patients with diabetes, which might be triggered directly, due to hyperglycaemia, or

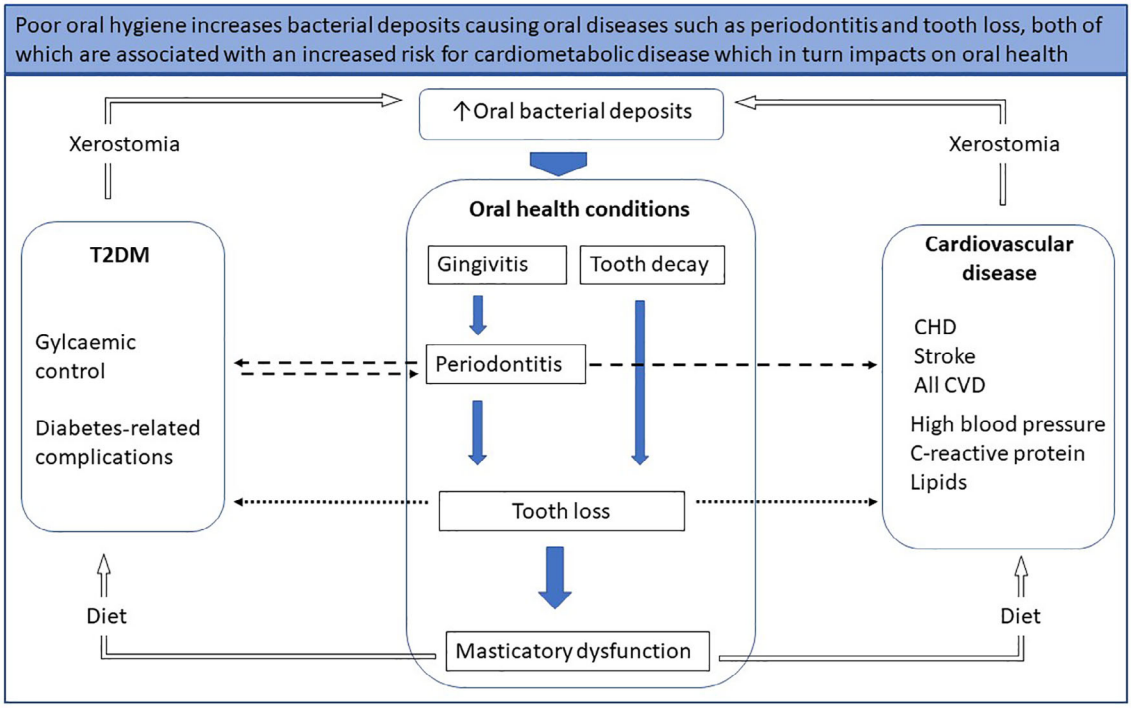

Figure 2 Summary of interrelationships between oral health conditions and cardiometabolic disease. Poor oral hygiene is the main driver of oral disease. Periodontitis is associated with an elevated risk for both cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM). The relationship with T2DM is bidirectional. Both diabetes and CVD increase the risk of xerostomia which in turn reduces bacterial clearance and contributes towards an increased risk of oral disease. Untreated oral disease results in tooth loss which in turn causes masticatory dysfunction impacting on diet and indirectly affecting cardiometabolic health. Tooth loss is also associated with an increased risk for CVD-related hospitalisations and is strongly associated with poor glycaemic control. CHD, coronary heart disease.

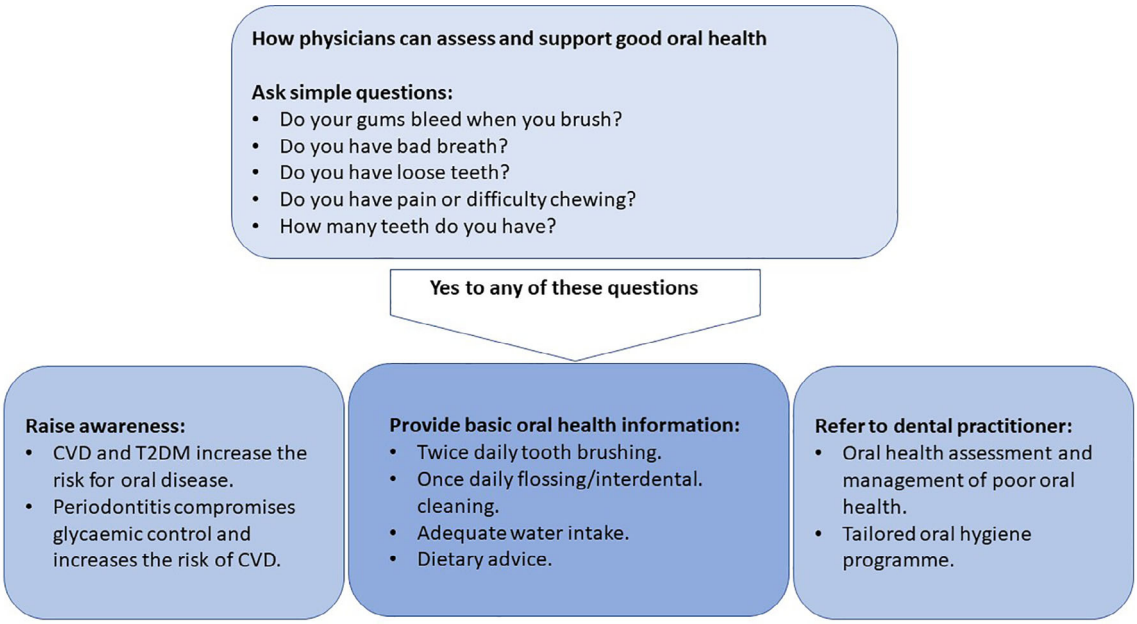

Figure 3 Guidance for the physician – How to assess and support good oral health. CVD, cardiovascular disease; T2DM, type 2 diabetes mellitus.

indirectly, due to medications used to treat T2DM and related cardiovascular conditions such as hypertension. Common antihypertensive drugs that reduce normal salivation include diuretics such as frusemide, beta-blockers such as atenolol, α2-adrenergic agonists such as clonidine, calcium channel blockers such as verapamil, and alpha-2 adrenergic agonists such as methyldopa.[25] Additionally, oral hypoglycaemics such as metformin can also cause xerostomia.[25]

Individuals with xerostomia might present with altered taste, mouth ulcers, cracked lips, difficulty chewing, swallowing, halitosis and in some cases a burning mouth sensation.[6] Mucosal tissues may appear dry, fissured or atrophic with the presence of a frothy viscous saliva. The implications of xerostomia for cardiometabolic health might be related to the elevated risk for tooth loss caused by the reduced buffering capacity of saliva. Tooth loss is associated with increased chewing time, deteriorated chewing function and poor dietary intake.[8]

Hyposalivation results in reduced bacterial clearance, thereby contributing indirectly to an increased risk for periodontitis.[6] The risk for tooth decay is also increased due to both the poor bacterial clearance and the reduced buffering capacity of saliva, which results in an acidic oral environment leading to dissolution of tooth structure.[6] This increased risk for both periodontitis and tooth decay increases the risk for tooth loss, which in turn affects chewing function.

Dental management of xerostomia focusses on reducing the risk for tooth decay, by the application of topical fluorides, which harden the tooth structure making it more resistant to decay. Additionally, treatment is aimed at reducing symptoms and maintaining chewing function by encouraging frequent consumption of tap water, using saliva substitutes/lubricants and chewing sugar-free gum to stimulate saliva production.[6] Identifying xerostomia in individuals with cardiometabolic disease and referral to a dental health practitioner allows management of the condition and will not only improve the patient's quality of life, but will reduce the risk of tooth loss and thereby maintain chewing function.

Conclusion

This review has discussed the associations between oral health conditions, such as periodontitis, xerostomia and tooth loss and cardiometabolic disease. Although the evidence on whether periodontal treatment can improve CVD endpoints is yet to be established, periodontal treatment has been shown to reduce surrogate markers of CVD such as pro-inflammatory cytokines, circulating lipids and blood pressure.[5] In diabetes this association has been shown to be bidirectional – individuals with diabetes having an increased risk of developing periodontal disease, and individuals with periodontal disease having an increased risk of developing diabetes.[23] Treatment of periodontal disease has been shown to improve

glycaemic control for patients with T2DM.[23] Diabetes and some of the medications used in the management of both T2DM and hypertension can contribute to the development of xerostomia. This can exacerbate periodontal disease and tooth decay, increasing the risk for tooth loss which contributes to masticatory dysfunction. In turn, this can have a negative impact on nutritional intake,[7] with the potential to further compromise the management of their underlying cardiometabolic disease. Significantly, tooth loss has been shown to be a predictor for both CVD events and poor glycaemic control[19–21](Fig. 2).

Many patients, especially those in older age groups with cardiometabolic disease, presenting to their medical practitioner will have underlying poor oral health. The focus needs to be on early diagnosis and prevention of oral disease. Therefore, patients with cardiometabolic disease should be advised of their increased risk for oral disease and that poor oral health can negatively impact on the management of their cardiometabolic health. They should be provided with simple oral health information and encouraged to see a dental practitioner regularly for an assessment of their oral health (Fig. 3). Early diagnosis and management of oral disease will reduce the systemic inflammatory burden thereby positively affecting cardiometabolic health outcomes, and help promote tooth retention, which in the long term will benefit nutritional intake and improve quality of life.

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