Periodontal disease and non-communicable diseases. Strength of bidirectional associations.

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SUMMARY

Periodontal disease (PD), along with cardiovascular and circulatory disease, diabetes mellitus, chronic respiratory disease and obesity, are globally regarded as some of the major non-communicable diseases (NCDs). The association between PD and these systemic illnesses is described as bidirectional. Gaining an understanding of the strength of the proposed associations between these diseases is important, as it will enable health professionals to identify common risk factors that will allow for synergistic prevention, diagnosis and management. To date, common preventive measures for NCDs include cessation of smoking, increased physical activity, healthy diets and sensible consumption of alcohol. Although risk factors such as smoking, inactivity, unhealthy diets and alcohol abuse are among the leading cause of tooth loss due to lifelong exposure, the prevalence of tooth loss is increasing in middle-income countries like South Africa. Hence the strength of the associations between PD and selected NCDs will be assessed, in order to generate guidelines for dental and other health professionals as well their patients to address the burden of disease associated with PD. Lastly, possible solutions to the problem will be addressed.

Keywords: periodontal disease, cardiovascular disease, diabetes mellitus, obesity, chronic obstructive pulmonary disease

ACRONYMS

AIDS:	Acquired Immunodeficiency Syndrome
BMI:	Body Mass Index
COPD:	Chronic obstructive pulmonary disease
CVD:	Cardiovascular disease
DALYs:	Disability-adjusted life years
EFP:	European Federation of Periodontology
HbA_{1c}:	Glycosylated haemoglobin
HIV:	Human immunodeficiency virus
NCDs:	Non-communicable diseases
OR:	Odds ratio
PD:	Periodontal disease
UN:	United Nations
WHO:	World Health Organisation

INTRODUCTION

Periodontal disease (PD) has been recognised as a major global public health problem due to its prevalence, economic impact on the health care system and health consequences.[1,2] Hence it is cited as one of the top six chronic non-communicable diseases (NCDs).[3] Prospective cohort studies provide evidence that PD is associated with an increased risk of premature death from any cause. This resulted in the formulation of a hypothesis that PD may be a risk factor for other diseases.[4] A global estimate regarding the prevalence of the 50 most common consequences of disease such as diabetes melitus,[5] found that chronic PD accounted for 10.8% of the population with NCDs, including chronic obstructive pulmonary disease (COPD), uncomplicated diabetes, as well as cardiovascular (CVD) and circulatory diseases. The association between oral, and especially metabolic systemic illnesses,[6] is described as bidirectional.[7] Disability-adjusted life years (DALYs), a measure of disease burden, provide evidence that the global burden of disease has continued to shift from communicable to NCDs. The prevalence of ischaemic heart disease became the leading cause of DALYs in 2010 when compared with 1990 (increase of 29%), followed by lower respiratory tract infections (44% decline). With regards to PD, the global DALYs for all ages showed a 57% increase for the same period.[8]

Identification of NCDs which are associated with PD and understanding the strength of the proposed associations are important, as it will enable health professionals to identify common risk factors in order to strive towards attaining synergistic control of these diseases.[9] Etiological and pathological links between PD and NCDs have also been suggested. This has resulted in global support towards the control of PD through approaches that address common risk factors.[1]

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Evidence generated from data related to 291 diseases amassed from 21 global regions, supports the association between PD and NCDs for cardiovascular disease (OR 1.1-2.4), type 2 diabetes mellitus (OR 1.5-2.3) and chronic respiratory tract diseases (OR 1.1-2.0). In addition, an association between obesity and PD has been suggested with both diseases being classified as NCDs.[8] To shed light on the strength of these associations, the 9th European Workshop in Periodontology resulted in the publication of a European Federation of Periodontology (EFP) Manifesto, calling upon dental and health professionals to act on the prevention, early diagnosis, and effective management of PD.[2]

The World Health Organisation (WHO) state that the top ten causes of mortality in South Africa, include diabetes mellitus (34.9%), HIV/AIDS (33.2%), lower respiratory tract infections (25.6%), hypertensive heart disease (16.6%), stroke (6.5%) and ischaemic heart disease (4.8%).[10] However, the NCD epidemic can be prevented through reduction of the underlying risk factors, early detection and timeous treatment.[11] In sub-Saharan Africa, infectious disease mortality rates are expected to decrease by 40% over the next 20 years, while NCD associated mortality rates will increase by 12%.[12] The latter underscores the fact that the prevalence of communicable diseases are decreasing while that of NCDs are increasing at a more rapid rate in low- and middle-income countries such as South Africa than in developed ones.[13] In addition, more than 80% of mortality and 40% of all disabilities are linked to heart disease, cancer, respiratory disease and diabetes.[12]

An extensive global focus on NCDs in 2011 lead to the United Nations (UN) High-Level Meeting on NCDs with the predominant emphasis being on heart disease, stroke, cancer, diabetes and chronic respiratory diseases.[14] The UN declared that NCDs are not only of concern for health, but also for development, as it acts as a barrier to development goals.[11,14] A South African national summit adopted a declaration that included a set of ten targets to be reached by 2020. NCDs that were addressed included cardiovascular disease, diabetes, chronic respiratory disease, and oral diseases as they are largely preventable through attention to four major risk factors that include smoking, physical inactivity, unhealthy diets and alcohol abuse.[11] The above was echoed by the WHO, indicating that this is ultimately the leading cause of tooth loss as result of tooth decay and PD, caused by lifelong exposure to these risk factors.[15]

According to the global World Health Survey, the prevalence of complete tooth loss is increasing dramatically in middle-income countries, especially among the poor and disadvantaged, with striking intra-country inequalities of complete tooth loss.[15] As South Africa is classified as a middle-income, transitional country where changes in dietary and activity patterns are occurring rapidly due to urbanisation and the resultant influences on nutrition, the findings of the global World Health Survey are of particular concern. The nutrition transition has resulted in an increase in the prevalence of overweight and obesity, not only a risk factor for developing NCDs,[16] but an NCD in its own right.[17-19] Urbanisation, industrialisation, economic transition and health services that are not always adequately equipped to deal with NCDs, are cited as being responsible for the increase in local morbidity and mortality rates.[11]

Cardiovascular disease

The proposed mechanisms linking PD to the development of CVD, are related to systemic inflammation, promotion of atherogenesis or provoking cardiovascular events,[20,21] such as angina, myocardial infarction, stroke and peripheral arterial disease.[21] Chronic PD results in the entry of bacteria or their by-products into the circulatory system. The host immune response reacts by favouring the formation, maturation and exacerbation of atheroma.[22,23] Another feasible hypothesis is that active aggressive PD is an important source of the endotoxemia that contributes to the onset of septic shock syndrome.[24] Whether the association between PD and CVD is independent and clinically significant, remains controversial.[20]

As a result, an investigation into the association between PD and CVD is of great importance, given the high incidence of both diseases and their related economic cost to society and the potential impact on public health should risk modification or therapeutic opportunities be identified. A statement issued by the American Heart Association indicated that common risk factors shared between the two conditions include smoking, increasing age and diabetes.[20,21] In addition, observational studies support an association between PD and atherosclerotic vascular disease, independent of known confounders.[25,26] However, a causal relationship is not supported. Despite a reduction in systemic inflammation due to periodontal treatment, marked by a reduction in CRP levels and an improvement in clinical measures of endothelial function in short term studies,[21] there is a paucity of evidence that a reduction in systemic inflammation prevents atherosclerotic vascular disease or modifies the outcomes.[20,21] Systematic reviews were conducted to investigate the effect of periodontal treatment on the prevention, and management or recurrence of cardiovascular disease in patients with chronic PD.[2,27] Only one appropriate study was found, yielding low quality evidence and hence rendering it insufficient to support or refute whether periodontal treatment can prevent the recurrence of cardiovascular disease in the long run amongst patients with chronic PD. In addition, no evidence regarding primary prevention was found.[27] Several animal models have demonstrated that the host's inflammatory response related to bacteria entering the blood stream favours atheroma formation, maturation and exacerbation.[28-30]

Consistent epidemiological evidence in turn, found that PD increases the risk for future cardiovascular disease, independent of other confounding factors.[31,32] While many studies have alluded to a positive association between PD and atherosclerotic vascular disease, others have yielded conflicting results, especially after adjusting for potential confounders.[33]

Guidance for patients with cardiovascular disease

Clinicians should be aware of emerging evidence regarding the relationship between PD and atherosclerotic CVD, independent of other risk factors.[34] Patients should be advised that PD places their general, as well as oral, health at risk. Based on current evidence, patients with PD and other risk factors for developing atherosclerotic CVD such as hypertension, overweight/obesity and smoking who have not undergone a medical examination in the past year, should be referred to a physician.[2] Controlling lifestyle-associated risk factors, including smoking cessation, nutrition counselling, and recommendations for

regular exercise, should be addressed within the context of comprehensive oral/periodontal treatment plans.[34, 35]

Diabetes mellitus

Prospective epidemiological studies confirm that PD increases the risk of poor glycaemic control, diabetic complications and associated morbidity.[2,35,36] In addition, susceptibility to PD in diabetics is increased threefold and there is a clear relationship between the degree of hyperglycaemia and severity of PD. The mechanisms that underpin the association between the two diseases are not completely understood. What is known, is that it involves aspects of immune functioning, neutrophil activity and cytokine biology.[37] Chronic hyperglycaemia and the accumulation of advanced glycation end products are due to an increased secretion of pro-inflammatory cytokines.[38] Some theories propose that advanced glycation end-products, changes in collagen formation, and altered immune function may facilitate the presence of bacteria in tissue. Effective treatment of PD is associated with a reduction in Glycosylated haemoglobin (HbA_{1c}) of approximately 0.4% at three months. This equates to adding a second drug to the pharmacological management of diabetes.[2,37] Type 2 diabetes is preceded by systemic inflammation, leading to reduced pancreatic ß-cell function, apoptosis and insulin resistance. Increasing evidence supports elevated systemic inflammation (acute-phase and oxidative stress biomarkers), resulting from the entry of periodontal organisms into the circulation, thus providing biologically plausible mechanisms which are responsible for the undesirable impact of PD on diabetes and its complications.[2] Consistent and robust epidemiological evidence demonstrates that severe PD adversely affects glycaemic control in diabetics and glycaemia in non-diabetics. In addition, there is a direct and dose response related effect between the severity of PD and diabetic complications. Emerging evidence also indicates an increased risk for diabetes onset in patients with severe PD.[37,39] Although the majority of research has focused on type 2 diabetes as a risk factor for PD, type 1 diabetes also increases the risk of PD. Accordingly, all patients with diabetes (including children and young adults), should be considered at an increased risk of PD.[37]

Guidance for patients with diabetes mellitus

Diabetic patients should be informed that the risk of PD is increased by poor glycaemic control. Furthermore, attaining glycaemic control may be more difficult in the presence of PD and in turn, can increase the risk for diabetic complications.[2,35] All newly diagnosed diabetics and patients with gestational diabetes, should receive an initial evaluation that includes a comprehensive periodontal examination with regular follow-up examinations as part of the ongoing management of the disease. For diabetic adolescents and children, annual oral screening is recommended from the age of six to seven years.[2]

Chronic obstructive pulmonary disease

There is emerging evidence for an association between PD and COPD such as chronic bronchitis and emphysema.[41] It appears to be a dose related effect, whereby more severe PD is associated with increasing loss of lung function.[27] The primary etiological factor is smoking,[4,41] modified by underlying inflammation,[43] likely caused by bacterial or viral infections or both.[44] In addition, PD and COPD share similar risk factors that include increasing age, obesity and a poor socioeconomic status.[42,43] It is considered plausible that the inflammatory response may be altered, either through aspiration or dental plaque and/or haematogenous diffusion or inflammatory mediators and plaque organisms from periodontal pockets.[44] Due to the relationship between the anatomical position of the oral cavity and the pulmonary tract, oral bacteria can easily be transported to the lungs, causing infection.[45]

The only evidence of causality is related to respiratory microorganisms that colonize the periodontal biofilm that may subsequently cause nosocomial pneumonia in mechanically ventilated patients. Epidemiological evidence supports a role of the periodontal biofilm acting as a reservoir for respiratory pathogens in patients with poor oral hygiene and PD and the resultant nosocomial pneumonia. Randomised controlled trials and a cross- sectional comparative study strongly support an improvement in oral hygiene as part of the prevention of nosocomial pneumonias and respiratory disease in acute care hospital environments and nursing homes.[47, 48]

Due to conflicting evidence generated by epidemiological studies investigating the relationship between PD and COPD, a meta-analysis was conducted to investigate this relationship. Findings based on random-effects meta-analysis were the existence of a significant association between PD and COPD (OR 2.08; $p<0.001$) with sensitivity analysis showing that the results were robust. The authors concluded that PD is a significant, independent risk factor for COPD. However, the causality of the relationship remains unclear.[46]

Studies investigating the relationship between PD and COPD remain preliminary, and large-scale prospective epidemiological studies are needed. Adequately powered randomised clinical trials that test the efficacy of periodontal interventions on the progression of COPD are required to further investigate the role of PD on its pathogenesis.[48] The association between dental plaque and pneumonia appears to be stronger than for dental plaque and COPD.[46,48]

Guidance for dental and other health professionals managing patients with respiratory disease

Improved oral hygiene reduces the risk of health care associated pneumonia as is suggested by several meta-analyses.[46,48] Based on data from five randomised controlled trials, it is recommended that staff responsible for caring for the elderly and/or frail, should be trained regarding the provision of basic oral hygiene for those who are incapable of self-care, and the implementation of twice daily oral hygiene in those capable of self-care. Hospital staff working in acute care environments should be trained on the use of antimicrobial and manual methods of reducing the oral microbial load in mechanically ventilated patients.[45,47]

Obesity

There is growing evidence regarding an association between PD and obesity.[49,50,51] An increase in the prevalence of obesity has resulted in an increased burden of NCDs such as diabetes, with recent evidence suggesting a possible link to PD.[35,36] Obesity is both an indirect risk factor for developing diabetes due to its effect on glycaemic control and a direct risk factor due to secretion of pro-inflammatory agents by adipose tissue that modify the periodontal reaction to the plaque biofilm.[36] Adipose cells secrete more than 50 bioactive molecules collectively known as adipokines that play a role in the regulation of inflammation, immunity and

insulin resistance. The immunologic activity of adipose cells is one of the main reasons why obesity is referred to as a chronic disease.[52] Given evidence that adipose tissue serves as a reservoir for inflammatory cytokines, it is possible that an increase in body fat increases the likelihood of an active host inflammatory response in PD.[40,52]

Those with a Body Mass Index (BMI) of ≥30 kg/m^2 (obese) were identified as having a significantly increased risk of developing PD when compared with those with a BMI of 18.5 to 24.9 kg/m^2 (normal weight).[50] This relationship is potentially mediated by insulin resistance.[53] A modest, positive association between obesity and PD is supported by the outcomes of two systematic reviews.[50,54] A meta-analysis of the systematic review found a significant association between PD and obesity (OR 1.35), resulting in a conclusion that a higher prevalence of PD should be expected among obese adults.[54] Another meta-analysis indicated statistically significant associations between PD and obesity (OR 1.81), overweight (OR 1,27) and a combination of overweight and obesity (OR 2.13), thus supporting an association between weight status and PD. The extent of this finding remains unclear.[50] It is possible that adiposity could be a marker for an unhealthy lifestyle resulting in an increased risk of PD and type 2 diabetes which may confound any association.[48] However, it is suggested that obesity might adversely affect PD, while there is little clinical evidence or biological plausibility that PD may affect obesity.[40]

Guidance for dental and other health professionals managing overweight/obese patients

It has been postulated that the prevalence of dentists may promise stronger primary health care resources and may highlight an opportunity for greater engagement of dentists in nutrition education and the prevention of obesity. Hence, the association between the number of dentists per capita and adult obesity rates were investigated. Findings were that having one additional dentist per 10 000 population was significantly associated with a one percent reduction in the prevalence of obesity ($p<0.001$) and was significantly larger in counties in which 25% of children or more, lived in poverty and in counties who had more primary care physicians per 10 000 population ($p \leq 0.0009$). The correlation between the prevalence of dentists and obesity highlights the potential for dental professionals as well as primary care providers to provide meaningful health education and support for improved nutritional behaviours.[55]

Additional prospective studies are needed to quantify and understand the mechanisms regarding the association between overweight/obesity and PD. A lack of evidence currently hampers the provision of guidelines to clinicians regarding the management of PD in overweight/obese adults.[50]

Factors affecting oral health

Globally the burden of oral disease is especially high among older individuals[40] and is strongly affected by social factors such as a low level of education, poverty, and poor housing.[55] Additional risk factors include an unhealthy lifestyle, high dietary sugar content, inadequate oral hygiene due to poor dexterity, smoking and excessive consumption of alcohol.[15] The current global patterns of oral disease reflects distinct risk profiles across countries, related to living conditions, behavioural and environmental factors, oral health systems, and implementation of schemes to prevent oral disease.[57]

Oral health care coverage is low in middle-income countries[6] and most low- and middle-income countries where the general population does not benefit from systematic oral health care.[57] Barriers to oral health care among older individuals include impaired mobility which hampers access to oral health care, particularly for those who reside in rural areas associated with a lack of public transport. This situation is worsened when oral health services and domiciliary care are not available. As some older individuals may experience financial difficulties following retirement, the cost or perceived cost of dental treatment, together with a poor attitude towards oral health, may deter them from visiting a dentist. In addition, the fear of violence may make them apprehensive of strangers, hindering good communication with oral health service providers.[15]

Potential solutions

Public health solutions to oral disease are most effective when they are integrated with those for other chronic diseases and with national public health programmes. The WHO Global Oral Health Programme aligns its work with the strategy of chronic disease prevention and health promotion.[6] The EFP Manifesto calls for a fundamental change in the perception of dental professionals' responsibilities regarding the achievement of patient general health and affirms that the patients' needs are best met through a collaborative approach between dental and medical professionals to provide coordinated multidisciplinary patient care, irrespective of where an individual enters the health care system.[2] Furthermore, there is growing appreciation that the dental team could play a key role in both the screening for NCDs and the promotion of healthy lifestyles, in particular amongst individuals who seek dental care but rarely consult a medical practitioner.[3]

Most chronic dental problems are highly dependent on daily self-care practice and compliance with preventive such as teeth brushing with fluoride toothpaste.[58,59] Meta-analyses and systematic reviews of oral health interventions point towards the absence or ineffectiveness of educational interventions for the prevention of oral disease.[60,61] In fact, conventional health education focusing on disseminating information and giving normative advice is insufficient to achieve sustained behavioural change.[62] Hence, transforming knowledge into actions which are beneficial and affordable to the population as well as creating opportunities and conditions that enable individuals and communities to enjoy good oral health is a great challenge.[61,63]

CONCLUDING REMARKS

The association between the PD and CVD remains controversial as, to date, a causal relationship is not supported. PD increases the risk of poor glycaemic control, diabetic complications and associated morbidity. In addition, susceptibility to PD in diabetics is increased and there is a clear relationship between the degree of hyperglycaemia and severity of PD. An association between PD and COPD such as chronic bronchitis and emphysema is supported by emerging evidence. Evidence regarding causality is related to respiratory microorganisms that colonize the periodontal biofilm, subsequently being responsible for nosocomial pneumonia in mechanically ventilated patients. The association between dental plaque and pneumonia appears to be stronger than for dental plaque and COPD. Obesity is both a direct and indirect risk factor for developing diabetes, thus suggesting that obesity might

adversely affect PD. However, there is a lack of evidence that PD may affect obesity. Additional prospective studies with the necessary statistical power are needed to quantify and understand the strength of the relationship between PD, CVD, diabetes, COPD and overweight/obesity in order to guide the prevention and management of these NCDs.

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