Professional Issues

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Metabolic Syndrome and Oral Markers of Cardiometabolic Risk

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Abstract

Metabolic syndrome is associated with increased risk of cardiovascular disease and type 2 diabetes mellitus. However, clinical diagnosis of metabolic syndrome alone does not permit proper assessment of cardiometabolic risk. Instead, it should be viewed as a modifiable risk factor. The development and progression of metabolic syndrome may be the result of many elements, with visceral obesity as a central component. Both metabolic syndrome and visceral obesity are linked to chronic inflammation, which leads to atherosclerosis and, thus, increases cardiometabolic risk. Obesity has been related to caries, traumatic injury, hyposalivation, tooth loss and periodontal diseases, and the latter have been associated with almost every feature of atherosclerosis. Thus, severe or refractory periodontal disease or a significant loss of teeth could serve as markers of cardiometabolic risk. Finally, there is growing evidence that saliva can reflect virtually the entire spectrum of normal and disease states; thus, we are likely to see increased use of saliva as a diagnostic tool and consequently, dentists may have a greater involvement in the identification and monitoring of non-oral disorders.

Metabolic syndrome is a cluster of factors associated with risk of developing type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD).[1] According to the International Diabetes Federation, metabolic syndrome is defined by the presence of visceral obesity (based on ethnicity-specific waist circumference criteria) plus any 2 of the following factors: hypertriglyceridemia, reduced high-density lipoprotein (HDL) cholesterol levels, hypertension and raised fasting glycemia (or T2DM).[2]

However, a clinical diagnosis of metabolic syndrome alone does not provide an assessment of cardiometabolic risk.[3] The latter (**Fig. 1**) may be defined as total risk of CVD resulting from the presence of traditional risk factors (age, family history, gender, smoking, high blood pressure, high cholesterol and diabetes) combined with the possible contribution of

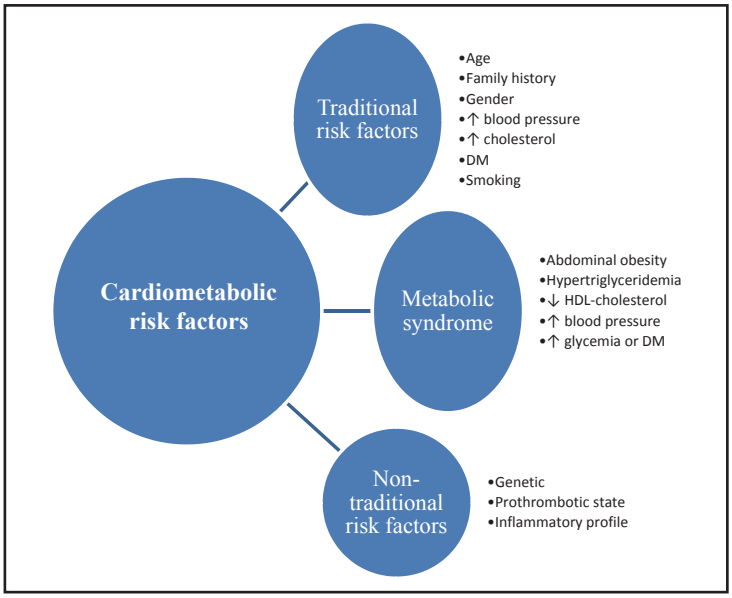

Figure 1: Assessment of cardiometabolic risk. Note: DM = diabetes mellitus, HDL = high-density lipoprotein

metabolic syndrome and non-traditional risk factors (genetic factors, prothrombotic state and inflammatory profile).[4] According to this definition, metabolic syndrome is a modifiable risk factor rather than a means to assess overall cardiometabolic risk.

Metabolic syndrome has received worldwide attention in the past few years because of its increasing prevalence: 20% to 30% of the adult population in almost all countries.[5] Metabolic syndrome is insidious in its development and is often diagnosed at a late stage, when signs and symptoms compel the affected person to seek medical care. For the most part, affected people ignore their condition, making preventive intervention of limited use. Thus, there is a need to find new ways to allow early assessment of cardiometabolic risk, and this cannot be achieved without the involvement of all first-line health care professionals.[4]

It has long been established that CVD and its treatment affect oral health.[6] In addition, numerous epidemiologic studies have associated common oral diseases, such as caries, xerostomia (hyposalivation), periodontal diseases and edentation (loss of teeth), with most elements of metabolic syndrome, T2DM and CVD.[7] Although these associations are not well understood, various physiologic mechanisms have been proposed to explain them. This suggests that dentists could be involved in the primary prevention and early assessment of cardiometabolic risk. Moreover, the close and regular relationship they maintain with an important part of the population over many years makes them valuable allies.[8] The objective of this article is to review the strength of evidence relating to oral diseases, metabolic syndrome and CVD and suggest some potential new oral markers of cardiometabolic risk.

Metabolic Syndrome, Cardiometabolic Risk and Inflammation

Metabolic syndrome results from complex interactions between various genetic and environmental factors. It contributes to atherosclerosis through a process of chronic and incremental damage to the arterial wall associated with hypercoagulability, oxidative stress, endothelial dysfunction and inflammation. Among these elements, the inflammatory process is of particular interest.[9,10]

Traditionally viewed as a lipid-based disorder, atherosclerosis is now considered to be an inflammatory disease. Not only does inflammation promote the initiation and evolution of atherosclerosis, but it also decisively contributes to precipitation of its acute complications. Indeed, a substantial proportion of cardiovascular events occur in people without the traditional risk factors and may be explained by the systemic low-grade inflammatory state associated with the presence of metabolic syndrome.[9,10]

Inflammation and Obesity

Obesity is the most prevalent nutritional disorder in industrialized countries.[11] However, there is a considerable heterogeneity in the associated health risk based on distribution of adiposity. Whereas accumulation of visceral adipose tissue is an important predictive factor of atherogenic disturbances, adipose tissue in the lower body is less associated with increased cardiometabolic risk.[4]

This explains the International Diabetes Federation's recommendation to measure waist circumference rather than body mass index (BMI) and recognizes visceral obesity as a central

component of the metabolic syndrome. Indeed, visceral adipose tissue, first thought to be an inert storage organ, is now viewed as a producer of a variety of molecules, named adipokines. These molecules have specific biologic functions[12-17] and affect energy metabolism by acting in an autocrine, paracrine and endocrine manner. Once in the portal circulation, adipokines are drained to the liver where they modulate the synthesis of hepatic proteins and trigger the development of an inflammatory milieu.[18] They have been linked to insulin resistance and vascular disorders.[19,20] These problems may be further exacerbated by the presence of traditional cardiometabolic risk factors.[21]

Commonly associated with such risk factors as dyslipidemia, T2DM and hypertension, obesity is now also known to interact with the inflammatory system. As both obesity and oral health are affected by nutrition, it is plausible that the oral condition reflects the systemic proinflammatory state associated with visceral obesity.

Obesity and Oral Health

There is a close relation between obesity and oral health. Obesity has been related to caries, hyposalivation and periodontal disease, all of which may cause loss of teeth, which may, in turn, alter food selection and contribute further to obesity.[22]

Epidemiologic studies find that edentulous men and women have, on average, higher BMI and greater visceral obesity than the dentate.[22] On one hand, tooth loss has been associated with diminished masticatory performance, food acceptability and perceived ease of chewing, which promote an obesogenic diet associated with higher intake of saturated fats or trans fatty acids rather than a healthy diet containing fibre, vegetables and fruits.[7] On the other hand, dental caries and tooth loss may also be the result of inadequate nutrition or lack of health awareness, which are often associated with fat accumulation.[7]

Obesity has also been associated with hyposalivation (reduced flow of saliva).[23] Although the causal relationship remains unknown, many explanations have been proposed, including an alteration in the major salivary glands similar to changes observed in the pancreas[24]; an inflammatory response in the salivary glands which affects their output capacity[25]; and an alteration of the hypothalamic–pituitary–adrenal axis and neuroendocrine regulation of the salivary glands due to the immune response.[26] Because saliva is essential for adequate functions such as chewing and swallowing, hyposalivation may trigger many oral problems. Normal salivation initiates digestion, enhances healing of mucosa and maintains oral flora balance. It diminishes the risk of developing dental decay through its buffer capacity. Saliva also protects tissues; without its lubricating effects, dentures do not adequately adhere to tissues and the oral mucosa becomes chafed and irritated.[27]

Very low saliva flow rate has been associated with a BMI > 25 in a cohort of adults under 50 years of age.[28] Furthermore, a reduced flow rate has been associated with childhood obesity[29] and T2DM.[30] These results indicate that a decrease in salivary flow may be the consequence of obesity or its associated systemic diseases rather than a local condition. Salivary hypofunction may also be the result of medications used to treat metabolic syndrome components, such as aspirin and antihypertensive and diuretic drugs.[31]

These observations have triggered an interest in sialometry (measurement of salivary secretion), and saliva is now increasingly being used in the monitoring of systemic diseases, particularly hypertension and T2DM.[24,32] Finally, it has been suggested that obesity, by its effect on immune parameters, could increase susceptibility to periodontal diseases.[33]

Association Between Periodontal Diseases and Cardiometabolic Risk

Periodontal diseases are a group of common chronic infections that produce an exaggerated inflammatory response to the oral pathogenic microflora. They affect the attachment of connective tissue and the supporting bone around the teeth, leading to tooth mobility and subsequent tooth loss.[34] In the past decade, the links between periodontal diseases and CVD have received growing attention because they share common risk factors, such as age, smoking, stress, low socioeconomic status, visceral obesity, diabetes and lack of health awareness.[35-37] Nevertheless, some observations suggest the involvement of

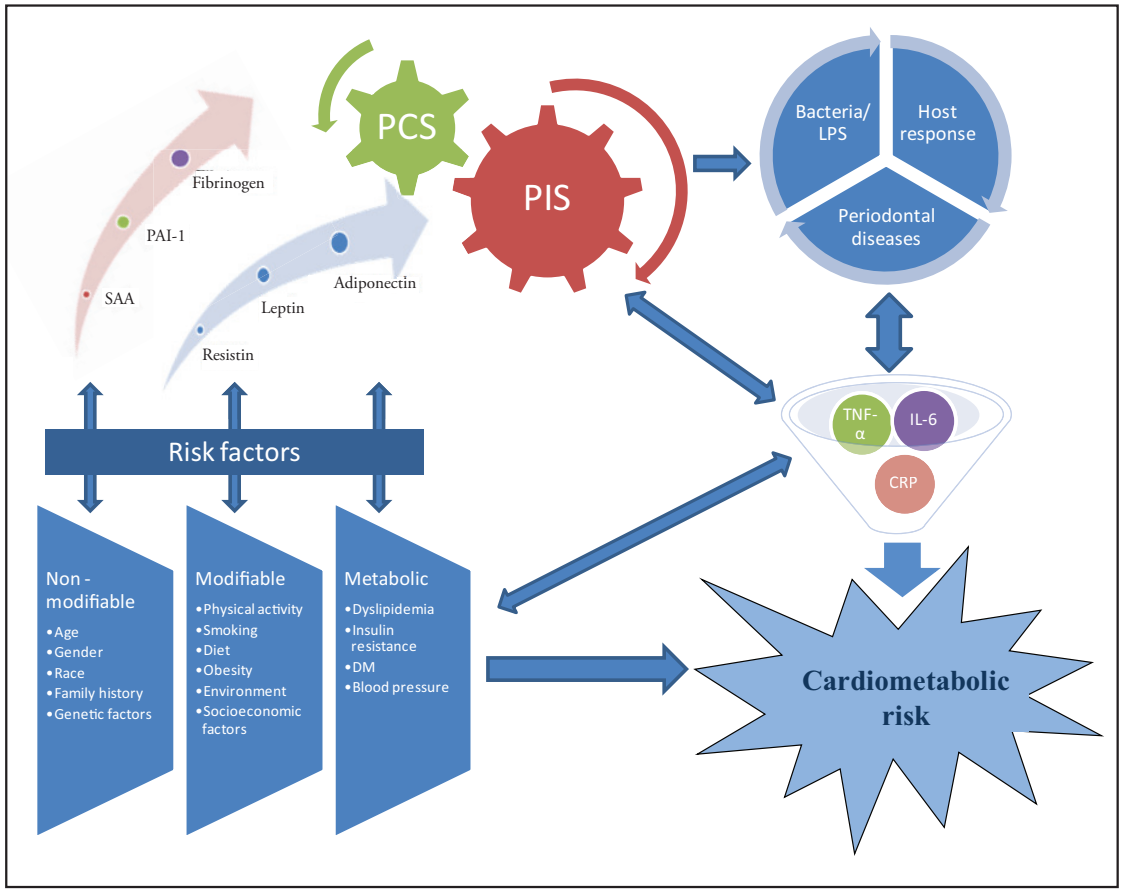

Figure 2: Relation between periodontal diseases and cardiometabolic risk. Note: CRP = C-reactive protein, DM = diabetes mellitus, IL-6 = interleukin-6, LPS = lipopolysaccharides, PAI-1= plasminogen activator inhibitor 1, PCS = procoagulation state, PIS = proinflammatory state, SAA = serum amyloid A, TNF = tumour necrosis factor.

pathophysiologic mechanisms beyond these traditional risk factors.

For a long time, periodontal diseases have been viewed as local infections with rare systemic implications. However, recently, the remote effects of periodontal diseases on systemic diseases have been investigated, and it has been suggested that this relation may be multidirectional (**Fig. 2**).[38] There is evidence that the inflamed epithelium of periodontal lesions forms an easy entry point that contributes to the dissemination of bacteria, their endotoxins (lipopolysaccharides) and all kinds of immune mediators that are produced locally.[35] Once in the circulation, they can exert effects on distant organ systems. In addition, studies have found positive associations between periodontal diseases and intima media thickness and dyslipidemia.[36,39] Moreover, common periodontal pathogens have been found in arterial plaques after endarterectomy,[40] and successful periodontal treatments appear to have beneficial effects on the control of diabetes, an important cardiometabolic risk factor.[41] Considering that obesity, metabolic syndrome, CVD and T2DM are major health problems worldwide, their association with periodontal diseases may be of great importance and deserves to be assessed and investigated in dental clinics.

Oral Markers and Cardiometabolic Risk

Despite the bulk of epidemiologic, experimental and clinical evidence supporting the association between oral health and cardiometabolic risk factors, there is little information about oral

biomarkers that could be used to assess cardiometabolic risk in clinical dental practice. Edentation should be considered, specifically when it is associated with visceral obesity.[7,22] Beyond tooth restoration and prosthetic adjustment, preventive care should include information about nutrition and exercise to improve overall health.[42] Because of the propensity of people with the metabolic syndrome to develop CVD, dentists must be aware of the close correlation between visceral obesity, a central component of metabolic syndrome, and periodontal diseases.[43]

People with severe chronic periodontal diseases represent 10%–15% of the population. Moreover, according to one study, approximately 50% of the variation in clinical severity of periodontal diseases would be due to genetic influence.[44] However, some researchers have also stated that oral inflammation that is unresponsive to the usual cleaning measures may indicate undiagnosed or uncontrolled T2DM.[45] Therefore, severe and treatment-refractory periodontal diseases could serve as oral markers of cardiometabolic risk.

Dentists should also be aware of the risk of systemic complications that may occur during dental procedures, question patients about their history and their symptoms and, if in doubt, consider referring these patients for medical evaluation before any invasive or stressful treatment. However, it is important to note that periodontal treatment leads to clinically relevant improvements in systemic inflammation and should be carried out as early as possible. Because the diagnostic criteria for periodontal diseases are not sufficiently specific, other oral markers should be investigated.

Recently, there has been growing appreciation that saliva can reflect virtually the entire spectrum of normal and disease states.[46] Many studies have shown that saliva is a reliable substance for diagnosing levels of steroids, hormones, drugs and antibodies,[47,48] and salivary diagnostics is an emerging field that has seen several important developments in the past decade.[49] Some of these may be relevant for the prognosis, diagnosis and management of periodontal diseases[50,51] and CVD.[52] For example, a saliva-based biomarker panel including C-reactive protein, myoglobin and myeloperoxidase has exhibited highly significant diagnostic capability for acute myocardial infarction.[49] Although these results remain to be validated for clinical applications, they suggest that saliva could be used to measure the levels of cardiometabolic risk markers in the near future and demonstrate the potential to identify and manage diseases.

Conclusions

Canadian dental clinics form a country-wide network for preventive care and dental treatment.[53] They are visited regularly by almost 80% of the general population,[54] and dentists routinely treat patients who do not have signs and symptoms of systemic diseases. In contrast, physicians are more likely to see their patients only when they present clinical manifestations of a systemic disease. Thus, Canadian dental clinics could assess public health issues other than oral diseases and successfully carry out cardiometabolic risk-factor screening. Once the diagnostic tools are validated, saliva collection could be carried out by the dental clinic network with the aim of reaching most of the general population.

Moreover, dentists could also be involved in screening and monitoring such common systemic disorders as metabolic syndrome, CVD and T2DM to reduce cardiometabolic risk in the population. We are thus moving from an era of single risk-factor intervention to a holistic management approach with multiple risk-factor interventions. As the fight against the metabolic syndrome epidemic will be difficult, many health professionals must be involved and, in this regard, dentists seem particularly well positioned.

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