

GRADUATION PROJECT

Degree in Dentistry

ASSOCIATION BETWEEN ORAL PATHOLOGIES AND METABOLIC SYNDROME

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RESUMEN

Introducción: El síndrome metabólico (MetS) es un conjunto de factores de riesgo como obesidad, hiperglucemia, hipertensión y dislipidemia que aumentan el riesgo de enfermedades cardiovasculares y diabetes tipo 2. Estudios recientes sugieren una relación bidireccional entre el MetS y las patologías orales, especialmente la periodontitis, lo que resalta la importancia de estrategias de manejo integradas para mejorar tanto la salud sistémica como oral. **Objetivos:** Este estudio exploró la relación bidireccional entre el MetS y las patologías orales, examinó cómo los componentes del MetS influyen en la salud oral (y viceversa), y evaluó si el manejo mejorado del MetS puede reducir la progresión de las enfermedades orales. **Materiales y Métodos:** Se realizó una revisión sistemática de 42 estudios clínicos revisados por pares publicados entre 2015 y 2025 a través de Medline Plus, PubMed y Google Scholar, indexados mediante la biblioteca UEM CRAI. Se incluyeron términos como “síndrome metabólico”, “obesidad”, “hiperglucemia”, “hipertensión”, “dislipidemia” y patologías orales como “periodontitis”, “caries dental”, “gingivitis”, “xerostomía” y “tumores orales”. Los estudios fueron seleccionados en inglés o español, con acceso completo al texto y relevantes para sujetos humanos. **Resultados:** Los hallazgos revelaron una asociación bidireccional significativa entre el MetS y las patologías orales. Los componentes del MetS aumentan el riesgo de enfermedades orales, mientras que la inflamación oral crónica puede agravar la disfunción metabólica. **Conclusión:** Existe un vínculo bidireccional entre el MetS y las enfermedades orales. El manejo integrado de ambas condiciones puede reducir la carga global de enfermedad y mejorar los resultados del paciente.

PALABRAS CLAVE

Odontología, trastornos metabólicos, patologías orales, inflamación oral-sistémica, vínculo dental con el síndrome metabólico

ABSTRACT

Introduction: Metabolic Syndrome (MetS) is a cluster of risk factors including obesity, hyperglycaemia, hypertension, and dyslipidaemia that elevate the risk of cardiovascular disease and type 2 diabetes. Recent studies suggest a bidirectional relationship between MetS and oral pathologies, particularly periodontitis, indicating the importance of integrated management strategies to improve both systemic and oral health outcomes. **Objectives:** This study aimed to explore the bidirectional relationship between MetS and oral pathologies, examine how MetS components influence oral health (and vice versa), and assess whether improved MetS management can reduce the progression of oral disease. **Materials and Methods:** A systematic review of 42 peer-reviewed clinical studies published between 2015 and 2025 was conducted through Medline Plus, PubMed, and Google Scholar, accessed via the UEM CRAI Library. Keywords included “metabolic syndrome,” “obesity,” “hyperglycaemia,” “hypertension,” “dyslipidaemia,” along with oral pathologies such as “periodontitis,” “dental caries,” “gingivitis,” “xerostomia,” and “oral tumours.” Inclusion criteria focused on English or Spanish-language clinical studies with full-text access and relevance to human subjects. **Results:** Findings demonstrated a significant bidirectional association between MetS and oral pathologies. MetS components were linked to increased risk of periodontal disease, xerostomia, and oral tumours, while chronic oral inflammation may exacerbate systemic metabolic dysfunction. Effective management of either condition positively impacted the other. **Conclusion:** This literature supports a strong, bidirectional link between MetS and oral diseases. Integrated care approaches addressing both systemic and oral factors may reduce overall disease burden and improve patient outcomes.

KEYWORDS

Dentistry, metabolic disorders, oral pathologies, oral-systemic inflammation, MetS dental link

1. INTRODUCTION

1.1. Metabolic Syndrome (MetS)

Metabolic syndrome (MetS) includes a group of conditions that together increase the likelihood of developing risk of cardiovascular diseases (CVD) and type 2 diabetes mellitus. The components of MetS comprises obesity, hyperglycaemia, hypertension and atherogenic dyslipidaemia (1). Additionally, factors such as age, ethnicity, hormonal imbalances, and non-alcohol-induced hepatic steatosis are acknowledged as contributors to an individual's increased susceptibility to MetS (1). It is critical to note that MetS is characterized by the presence of at least three of the aforementioned conditions, with the specific combination varying across individuals (1, 2).

According to the National Institutes of Health (NIH), the prevalence of MetS across Europe was 24.3% among 8,468 selected study participants, with rates of 23.9% in men and 24.6% in women (2). The study further demonstrated an age-related rise in prevalence across all cohorts, alongside a marked increase in MetS prevalence over the past few decades, attributed to lifestyle changes (2, 3).

1.2. Components of MetS

1.2.1. Obesity

Obesity, the most frequently observed component of metabolic syndrome, involves excessive intra-abdominal fat accumulation, which contributes to clustered cardiometabolic risk factors (3, 4). It can be caused by a variety of factors, including an excessive consumption of high-fat diet, genetic conditions, lack of physical activity and cultural influences (4). It is considered a component of MetS when individuals present a waist-centered obesity of >102 cm in men and >88 cm in women. It is understood that abdominal obesity is usually accompanied with glucose intolerance, dyslipidaemia and hypertension, which are all components leading to MetS (4).

Additionally, the rising prevalence of obesity is identified to be a major global health concern. According to Keaver et al., obesity is expected to affect 89% of men and 85% of women by 2030. This ultimately causes a 97% rising prevalence of coronary heart disease (CHD) associated with obesity, a 21% rise in type 2 diabetes cases, and a 61% increase in cancer rates (4).

1.2.2. Hyperglycaemia

Hyperglycaemia originated from the Greek is a terminology referring to high blood sugar, in which records higher than 125 mg/dL fasting level and exceeding 180 mg/dL after 2 hours postprandially (5). It is identified that certain physiological factors contribute to hyperglycaemia in which includes, decreased insulin secretion, reduced glucose utilization and escalated glucose production, in which all evoke a disturbance in the glucose homeostasis (5). It is further distinguished that there lie several secondary causes in which trigger hyperglycaemia. This includes an obliteration of the pancreas, a vital organ in charge of insulin production, due to diseases including but not limited to pancreatitis, hemochromatosis and cystic fibrosis. In addition, it is also highlighted that endocrine disorders such as the Cushing syndrome, pheochromocytoma and acromegaly are also secondary causes of hyperglycaemia as they evoke a peripheral insulin resistance (5,6). Furthermore, the intake of certain medications such as glucocorticoids, phenytoin and oestrogens are also discerned to be secondary causes of hyperglycaemia (5,6).

Along as well, it is perceived that the occurrence of hyperglycaemia has increased significantly over the past two decades, driven by major risk factors such as increased obesity, decreased physical activity, type II diabetes and an aging population (4, 6). Furthermore, it is also discerned that hyperglycaemia is more prevalent among low- to middle-income households, recording highest in countries like China, India, United States, Brazil, and Russia (6). Furthermore, according to the recent findings from the Centres for Disease Control and Prevention (CDC), around 30.5 million Americans suffer from dysglycaemia, particularly hyperglycaemia, and nearly 84 million are affected with prediabetes,” hence highlighting the overburden this phenomenon holds worldwide (6).

1.2.3 Hypertension

Hypertension, widely prevalent in the general population, is a key component of metabolic syndrome. It is defined by consistently elevated systolic blood pressure (SBP) surpassing 140 mmHg and/or diastolic blood pressure (DBP) above 90 mmHg in both clinical assessments and typical home monitoring (7). A large proportion of hypertension cases are classified as essential, meaning they have no identifiable cause. Elevated salt intake has long been implicated as a contributing factor, particularly among individuals genetically predisposed to salt sensitivity (7,8). The pathogenesis of essential hypertension involves several interrelated mechanisms, including enhanced sodium retention leading to fluid overload, dysregulation of the renin-angiotensin-aldosterone system (RAAS), and increased activity of the sympathetic

nervous system. These processes collectively raise total peripheral resistance and cardiac afterload, culminating in sustained high blood pressure (7,8).

Furthermore, high blood pressure is a significant public health concern and a leading global risk factor for mortality, with hypertension-related deaths rising from 6.8 million in 1990 to 10.8 million in 2019 (8). The World Health Organization (WHO) reported that, in 2019, approximately 33% of adults aged 30–79 years were affected by hypertension, which translates to around 1.3 billion individuals, based on age-standardized prevalence estimates. This drastic increase is noted to be due to several well-established risk factors such as genetic predisposition, excessive sodium consumption, smoking, physical inactivity, obesity, and alcohol consumption (8).

1.2.4 Dyslipidaemia

Dyslipidaemia is characterized by abnormal lipid levels in the bloodstream, representing a significant risk factor for cardiovascular diseases (CVD) (9). Dyslipidaemia is a fundamental aspect of metabolic syndrome, as its diagnostic criteria include hypertriglyceridemia (serum triglycerides ≥ 150 mg/dL) and low, high-density lipoprotein (HDL) cholesterol levels (HDL-C < 35 mg/dL for males and < 40 mg/dL for females, according to WHO) (9). People with metabolic syndrome, particularly those with abdominal obesity, tend to have a lipid profile that is highly atherogenic, contributing to their elevated CVD risk. Central fat accumulation and insulin resistance are closely linked to a group of dyslipidaemia abnormalities, this includes raised plasma triglyceride levels, higher concentrations of very-low-density lipoprotein (VLDL) and intermediate-density lipoprotein (IDL), the existence of small, dense LDL particles, and lower levels of HDL cholesterol. These disturbances in lipoprotein metabolism tend to co-occur rather than appear in isolation, forming core characteristics of metabolic syndrome (9,10).

Moreover, dyslipidaemia is recognized to be a major global public health issue, affecting millions of people and heightening the risk of cardiovascular diseases (10). Furthermore, its epidemiology varies based on region, age, sex, and ethnicity, affected by both genetic and environmental factors. In the case of an individual suffering from hypercholesterolemia, the prevalence of dyslipidaemia is noted to range from 20–60% (10). Whereby, an individual presenting obesity even marks a higher percentage of 60–80%, whilst recording over 80% in the presence of other cardiovascular disease risk factors (9, 10). In patients with diabetes its prevalence is varied with values ranging from 60–90%, and in cases with prediabetes, although prevalence rates vary widely, they tend to be higher than those observed in the general

population, hence highlighting how the different components of Mets interconnect inevitably (10).

1.3. Oral Pathologies

1.3.1. Dental caries

Dental caries, or tooth decay, is characterized by the localized demineralization of the hard tissues of the teeth due to acids produced from food residues or sugars (11). The presence of decay is identified when a brown-black lesion is found on a pit, fissure, smooth surface, or when there is a visibly softened area on the floor and/or wall of the tooth's crown or root. Henceforth, it is recognized as a cumulative and progressive condition, as the breakdown of tooth structure due to an irreversible decay and necessitates restorative intervention and continuous maintenance to preserve dental health (11).

According to the WHO, around 2.4 billion people, or 35.3% of the global population, have tooth decay in their permanent teeth (11). Additionally, approximately 621 million children, or 9.02% of the global population, are affected by decayed primary teeth. These figures highlight that dental caries is a widespread issue that affects individuals across all age groups throughout their lives (11).

1.3.2. Periodontitis

Periodontitis, a chronic inflammatory disease resulting from the build-up of dental plaque biofilm, where an imbalance in microbial populations triggers a sustained and harmful inflammatory reaction (12). This leads to significant tissue damage, such as the deterioration of the periodontal ligament, the formation of deep pockets, and the loss of alveolar bone, all primarily driven by the body's immune response to the bacterial challenge presented by the biofilm (12).

The occurrence of periodontitis is high, with estimates showing it affects 20-50% of the global population, both in developed and developing countries. This widespread issue across various age groups, from adolescents to older individuals, underscores the significant public health burden it represents (12, 13). A variety of factors contribute to the onset of periodontitis, including smoking, inadequate oral care, diabetes, medication usage, aging, genetic susceptibility, and stress. Furthermore, extensive research demonstrates the strong link

between periodontal disease and systemic health conditions like cardiovascular disease and diabetes, highlighting the importance of oral health for overall health (13).

1.3.3. Gingivitis

Gingivitis is identified to be an inflammatory condition affecting the gingival tissue, primarily resulting from bacterial infection (14). On the contrary to periodontitis, it does not involve attachment loss or displacement of the junctional epithelium. Instead, the inflammation is confined to the gingival epithelium and the underlying connective tissue (13, 14). It is the most common form of periodontal disease and can present in different ways depending on its duration, severity, and the underlying causes. The most prevalent form is the chronic plaque-induced variety. The typical signs of gingivitis include swollen, red, and tender gums, a shiny appearance, and bleeding when the gums are lightly probed (14).

The epidemiology of gingivitis is distinguished to be more occurring in the male population compared to females as women tend to maintain better oral health routines. Furthermore, various research studies have illustrated that gingivitis is more prevalent among individuals with lower socioeconomic status, as those of higher status tend to have a more proactive approach to oral hygiene maintenance and greater access to healthcare services (14,15). Additionally, studies indicate that gingivitis is highly usual in pregnant women, with more severe forms of the condition frequently observed during pregnancy (15).

1.3.4. Xerostomia

Xerostomia, commonly known as "dry mouth," is a medical condition in which an individual suffers difficulties in eating, swallowing, speaking, halitosis, and altered taste perception all in which severely impacts the patient's way of life (16). This condition may be linked to changes in the composition of saliva and decreased salivary flow. However, it is often associated with reduced salivary gland function and is more commonly observed in older individuals taking anti-hypertensive medications (16). These anti-hypertensive medications are identified to be beta-blockers (propranolol), calcium channel blockers (nifedipine) and various angiotensin-converting enzyme inhibitors (captopril). The cause is studied to stem from the stimulation of the central nervous system and alpha-2 adrenergic receptors in the salivary glands due to these drugs, resulting in a decreased H₂O secretion, by obliterating Ca²⁺ channels (16,17).

Xerostomia is a significant yet often overlooked condition, both by the general population and healthcare professionals. Its prevalence has been reported to range from 5.5% to 46%, with

notable variations based on age and gender. This is largely attributed to the fact that older individuals are more likely to be prescribed with anti-hypertensive and or psychotic medications, which can contribute to the development of xerostomia (17).

1.3.5. Oral cancer

Oral cancer defined to be a malignant neoplasia, appearing externally on the lip or internally in the oral cavity (18). Conventionally, it is identified as a oral squamous cell carcinoma (OSCC), as in the field of dentistry, 90% of cancers are histologically derived from squamous cells, most commonly affecting the lips, tongue, floor of the mouth, and gums (18). Oral cancer represents a significant public health challenge worldwide, particularly for dental practitioners. It ranks within the top 10 cancers by incidence, and despite progress in research and treatment, survival rates have seen little improvement in recent years, highlighting the crucial need for early prognosis and prevention (18, 19).

Oral cancer occurs two to three times more frequently in men than in women across most ethnicities. When combined, oral cavity and pharyngeal cancers rank as the sixth most prevalent cancer globally (19). According to the latest data from the International Agency for Research on Cancer (IARC), the annual incidence of oral cancer has risen to over 300,000 diagnosed cases, with around 145,000 deaths annually. This showcases the critical need to understand its causal agents and implement early preventive strategies (19).

1.4. Shared risk factors between MetS and oral pathologies

1.4.1. Diet

Many research studies have confirmed the existence of correlations between an unhealthy diet and the presence of MetS (20). It is distinguished that people suffering from metabolic syndrome have showcased a diet constituting of refined flour products, foods high in trans-fat, sugar, and red meat, whereby the consumption of vegetables, fruit, fish and dairy products are limited. All these have been analysed to ultimately result in increased glucose and triglycerides concentration, as well as high concentration of LDL cholesterol (20).

Similarly, diet has also been linked as a risk factor to several oral pathologies particularly dental caries, primarily a diet containing excessive sugar and carbohydrate intake (21). Bacteria in the mouth (ex: *Streptococcus mutans*) metabolize sugars from foods like candy, soda, and processed snacks, producing acids that erode tooth enamel, henceforth evoking

demineralization (21). Frequent snacking prolongs acid exposure, while a lack of essential nutrients such as calcium, phosphorus, and vitamins weakens enamel and hinders repair. Additionally, inadequate intake of fibrous fruits and vegetables reduces saliva production, which is crucial for neutralizing acids and clearing food debris (21).

1.4.2. Lifestyle factors

The development of MetS is influenced by smoking (≥ 20 g tobacco/day) and excessive alcohol consumption (>1 drink/day) as they promote insulin resistance, dyslipidaemia, hypertension, and obesity. Smoking lowers insulin sensitivity raises LDL cholesterol and triglycerides and increases blood pressure through nicotine-induced stress response (22). Similarly, alcohol disrupts fat metabolism, raises triglycerides, and contributes to weight gain, particularly abdominal obesity. Both also trigger inflammation and oxidative stress, further impairing metabolic function, henceforth raising the risk of CVD and type 2 diabetes (22).

Correspondingly, smoking and alcohol consumption are significant risk factors for various oral pathologies, including oral cancer and periodontal disease (23). Smoking promotes the development of oral cancer, particularly OSCC, by exposing the mouth to carcinogens, weakening the immune response, and impairing wound healing (23). It also evokes periodontal disease by encouraging plaque buildup, reducing blood flow to the gums, and weakening the body's defence mechanisms, leading to inflammation and tooth loss. Likewise, excessive alcohol, evoking the risk of oral cancer by acting as a solvent for harmful substances and contributing to dry mouth (xerostomia), which in turn raises the likelihood of dental caries and other oral infections (23).

1.4.3. Genetic predisposition

It is understood that heritability estimates for each of the MetS traits exceed 50. Consequently, genetic variations can affect how the body processes fats, regulates blood sugar, and manages fat storage, leading to an increased likelihood of central obesity and impaired metabolic functions (4, 5, 24). Furthermore, research has demonstrated that some individuals inherit genes associated with reduced sensitivity to insulin, which can ultimately lead to insulin resistance and eventually type 2 diabetes (24).

Similarly, genetic predisposition plays a vital role in the primary development and progression of various oral pathologies, notably periodontal disease (12, 25). Various genetic variations can influence the immune response, inflammation, and the body's response to oral bacteria, exposing some individuals to a higher risk of severe gum diseases (25). Particular variations

in genes related to immune regulation, such as cytokine production, can lead to a heightened inflammatory response, accelerating the progression of periodontal disease in genetically predisposed individuals (25).

1.5. Biological mechanisms linking MetS and oral pathologies

1.5.1. Chronic inflammation as a shared pathway

Chronic inflammation is a key shared pathway between metabolic syndrome and oral pathologies, acting as a central mechanism that links these two conditions (25, 26). In metabolic syndrome, chronic low-grade inflammation is driven by factors such as insulin resistance, obesity, and dyslipidaemia, leading to increased levels of pro-inflammatory cytokines and oxidative stress (25,26). Similarly, oral pathologies, such as periodontal disease, are characterized by chronic inflammation in response to bacterial infection, which also triggers the release of pro-inflammatory molecules (26). This inflammation not only damages tissues but also exacerbates systemic inflammation, creating a cycle that worsens both metabolic syndrome and oral health. The inflammatory processes in both conditions are interconnected, with periodontal disease potentially contributing to the development of metabolic syndrome, and vice versa, thereby highlighting the significance of addressing inflammation in managing both health issues (26).

1.5.2. Role of the oral microbiome in systemic health

The oral microbiome is a key factor in bridging the gap between MetS and oral health issues. Dysbiosis, which occurs when the oral microbiome is out of balance, can facilitate the growth of harmful bacteria that promote chronic inflammation, which exacerbates both periodontal disease and systemic conditions associated with MetS, such as insulin resistance and dyslipidaemia (27). These inflammatory responses can enter the bloodstream, contributing to the low-grade systemic inflammation that characterizes MetS. Additionally, certain oral bacteria are linked to impaired insulin sensitivity and fat accumulation, further intensifying metabolic disturbances. Thus, maintaining a healthy oral microbiome is essential for preventing the interconnection between oral health and metabolic disorders (27).

1.6. Impact of MetS on oral health

MetS has a significant impact on oral health, primarily through its association with chronic systemic inflammation, insulin resistance, and dysregulated lipid metabolism (25, 9, 28). The persistent low-grade inflammation seen in MetS enhances the inflammatory response in periodontal tissues, increasing the risk of periodontal diseases such as gingivitis and periodontitis (28). Insulin resistance, a central feature of MetS, impairs the function of neutrophils and reduces the immune system's ability to combat bacterial infections, further leading to periodontal destruction. Additionally, individuals with MetS often present with altered salivary flow and composition, contributing to xerostomia, which increases susceptibility to dental caries and oral infections (28). Dyslipidemia associated with MetS also promotes atherosclerotic changes in the vasculature of the oral tissues, which can impair tissue healing and exacerbate periodontal tissue breakdown (9, 28). Consequently, the systemic manifestations of MetS not only contribute to an increased burden of oral diseases but also complicate their management, highlighting the need for integrated care approaches targeting both systemic and oral health (28).

1.7. Impact of oral diseases on MetS and systemic health

Oral diseases, particularly periodontal disease, have been shown to negatively affect MetS and overall systemic health (29). Chronic periodontal infections lead to the release of pro-inflammatory cytokines, such as interleukins and tumor necrosis factor-alpha, into the bloodstream. These inflammatory markers facilitate systemic inflammation, which can lead to insulin resistance, a central component of MetS (29). Additionally, periodontal disease has been linked with elevated levels of C-reactive protein (CRP), a biomarker of inflammation, which further enhances metabolic dysregulation (25, 26, 29). Studies suggest that oral infections can lead to the worsening of other MetS components, including dyslipidemia, hypertension, and abdominal obesity, by triggering systemic inflammatory responses that interfere with metabolic processes. Furthermore, untreated oral diseases may impair the body's ability to manage glucose and lipid metabolism, increasing the risk of developing cardiovascular diseases. Thus, maintaining oral health is crucial for managing MetS and preventing its progression to more severe systemic complications (29).

1.8. Prevention and treatment of Mets and oral pathologies

Prevention and treatment of MetS and oral pathologies require a multi-faceted approach that addresses both systemic and oral health (30). For MetS, lifestyle modifications are fundamental, including dietary changes such as reducing sugar, salt, and unhealthy fats, alongside increasing fibre intake and promoting regular physical activity to improve insulin sensitivity, reduce obesity, and regulate blood pressure. Pharmacological interventions, such as antihypertensive medications, statins, and insulin sensitizers, may also be necessary for managing MetS components (30).

In terms of oral health, sustaining proper oral hygiene through daily brushing, flossing, and professional dental cleanings is essential in preventing periodontal diseases. For individuals with MetS, more frequent dental checkups may be required to monitor and manage periodontal conditions (30,31). Additionally, addressing risk factors such as poor diet, smoking and exorbitant alcohol consumption can further prevent both systemic and oral health complications. Regular screening for oral diseases and preserving a healthy oral microbiome can help diminish the impact of oral pathologies on MetS and vice versa. It is understood that integrated care that combines dental professionals with healthcare providers is vital for effective prevention and management (31).

1.9. Justification

An individual suffering from metabolic syndrome possesses an amplified risk of developing CVD and type 2 diabetes (1). However, it is understood that MetS is not just alarming for the human body but also for the oral cavity, as it is the prime suspect behind major oral pathologies including but not limited to dental caries, gingivitis, periodontitis and even oral cancer (29). Consequently, comprehending the medical components that make the constellation of MetS aids in the early diagnosis and potentially preventing the oral pathologies it may eventually provoke, whilst integrating preventive strategies and treatment plans addressing both oral and general health (3, 28).

2. OBJECTIVES

2.1. Primary objective

- To investigate literature reviews to assess whether metabolic syndrome contributes to an increased risk of developing oral pathologies and vice versa

2.2. Secondary objectives

- To assess the components forming the constellation of MetS and establishing their association with oral pathologies and vice versa
- To determine if improved management of metabolic syndrome can reduce the incidence and progression of oral pathologies in affected individuals and vice versa

3. MATERIALS & METHODS

This dissertation on the association between oral pathologies and metabolic syndrome, was based off various comprehensive literature reviews focused on the following keywords: “metabolic syndrome”, “obesity”, “hyperglycaemia”, “hypertension”, “dyslipidaemia”, “dental caries”, “periodontitis”, “gingivitis”, “xerostomia”, “oral tumours”. It was strictly ensured for all articles to be inclusive in a published date of maximum 10 years span (2015-2025), to ensure information obtained is the latest advanced finding in the field. The initial search yielded an initial collection of 57 articles, in which were refined to 34 for final inclusion, following specific criteria to maintain relevance.

These articles were sourced from electronic databases available through the UEM CRAI Library, with a primary focus on Medline Plus, PubMed, and Google Scholar. These platforms offered a wide range of peer-reviewed literature, ensuring the credibility and relevance of the selected studies to the research topic. The exact search strategy through these platforms was illustrated in a table for further clarity (Annex 2).

The articles found were scanned for suitability followed by an inclusion and exclusion criteria:

Inclusion criteria	Exclusion criteria
1. Articles released within the last 10 years (2015-2025) 2. Articles in English and Spanish 3. Title and abstract in relevance to the content of the research 4. Full articles available 5. Clinical trials on human subjects 6. Extensive clinical studies	1. Articles published more than 10 years ago 2. Articles written in any language other than English & Spanish 3. Title and abstract irrelevant to the content of the research 4. Article not fully available 5. Reviews and meta-analysis 6. Editorials lacking original data

Table 1: Inclusion and exclusion criteria regarding this research.

4. RESULTS

4.1. Flowchart

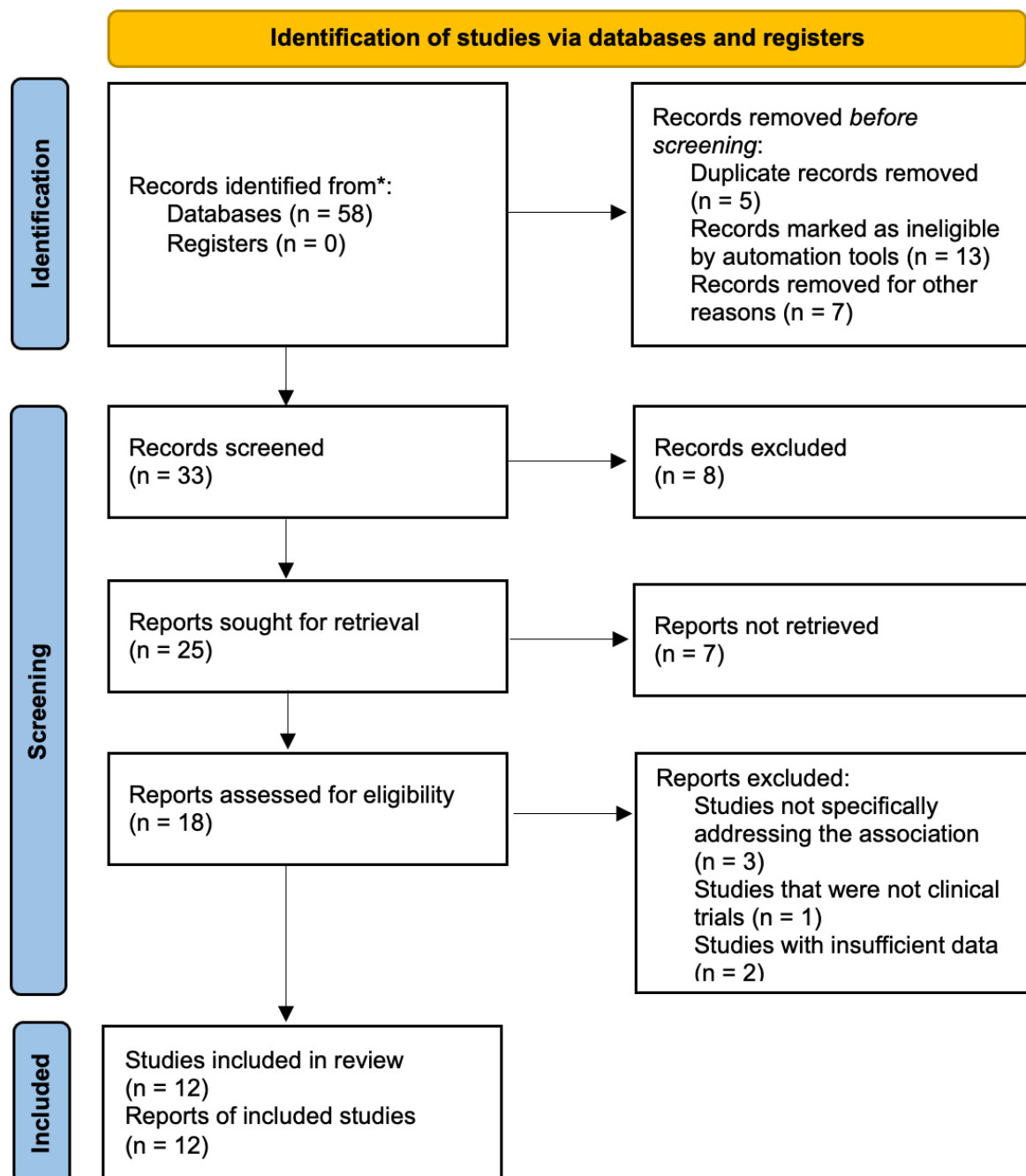


Figure 1: PRISMA 2000 flowchart diagram

PRISMA 2000 Flow diagram - Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71.doi: 10.1136/bmj.n7.

4.2. Table of Results

The 12 articles found were categorized into 3 different tables based on the type of study done: case control, cross-sectional, cohort and randomized clinical trials. Furthermore, to study the quality of assessment in each article, the risk of bias was studied using the Newcastle-Ottawa scale (Annex 3), with the only exception of the randomized clinical trials which were assessed by Cochrane risk-of-bias tool (Annex 3).

A. Case-control Study					
Author & Year	Country	Sample Size & Age Range	Oral Pathology Evaluated	Main Findings	Risk of Bias
Lulëjeta Ferizi et al., 2022 (32)	Kosovo	80 participants - 34 children with good metabolic control - 46 children with poor metabolic control	Dental caries & periodontitis	- Altered salivary composition in poor metabolic group led to more dental caries. - Poor metabolic control increased susceptibility to gum disease - Poor glycaemic control delayed wound recovery and raised infection risk. - Bidirectional relationship: Metabolic disturbances and oral health issues influenced each other.	Moderate
		10-15 years			

B. Cross-sectional Studies					
Author & Year	Country	Sample Size & Age Range	Oral Pathology Evaluated	Main Findings	Risk of Bias
Takashiro Iwasaki et al., 2019 (33)	Japan	1,106 participants	Dental caries	- Higher dental caries experience (measured by decayed, missing, filled, teeth (DMFT) scores) was significantly linked with an increased prevalence of MetS. - The relationship between caries and MetS remained as prevalent even after adjusting for dietary habits.	Moderate
		40-74 years			
Farhad Moradpour et al., 2023 (3)	Iran	10,000 participants	Periodontitis	- Higher prevalence of chronic periodontitis in individuals with MetS. - Systemic inflammation and insulin resistance linked to poor oral health, especially periodontal disease.	Low
		35-70 years			

				• Tooth loss is more common among those with MetS. • Bidirectional relationship between MetS and oral health, with oral health worsening systemic inflammation.	
Miki Kikui et al., 2017 (34)	Japan	1,108 participants	Periodontitis	• Significant association was highlighted between abdominal obesity and periodontal disease. • Strong association was identified between hyperglycaemia and periodontal disease. • Participants with hypertension showed a higher prevalence of periodontal disease. • An independent significant association was observed	Moderate
		30-79 years			

				between dyslipidaemia and periodontal disease.	
Kyeong-Soo Lee et al., 2015 (35)	South Korea	941 participants	Gingivitis	- A higher number of positive MetS parameters is linked to an increased risk of gingivitis. - Low HDL cholesterol (dyslipidaemia) showed a strong correlation with gingivitis.	Moderate
		12-18 years			
K. Ka et al., 2017 (36)	Canada	219 participants	Gingivitis	- MetS was associated with increased gingival inflammation in obese boys, shown by higher tumour necrosis factor-alpha (TNF-α) levels in gingival crevicular fluid (GCF). - No such correlations were found in obese girls.	High
		8-10 years			
Alba Pérez-González et al., 2021 (37)	Spain	354 participants	Xerostomia	MetS is associated with an increased risk of gingivitis and xerostomia.	Moderate
		Adults (not specified)			

				• Obese individuals, especially those with MetS, are more likely to experience xerostomia. • Higher risk of dry mouth is linked to MetS and obesity, impacting overall oral health, highlighting a bi-directional relationship	
Nattapat Khongsirisombat et al., 2021 (38)	Thailand	71 participants (44 with MetS and 27 healthy subjects) 60-86 years	Xerostomia and oral-health related quality of life (OH-QoL)	• Xerostomia was notably higher in MetS patients. • MetS patients experienced worse OH-QoL, influenced by tooth disease and xerostomia. • Shorter sleep duration (≤ 6 hours) was linked to poor OH-QoL. • Waist circumference (WC) and sleeping hours	High

				were key factors contributing to negative OH-QoL in MS patients. • Higher WC correlated with poorer OH-QoL, potentially due to obesity and increased risk of diabetes mellitus	
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C. Cohort Studies					
Author & Year	Country	Sample Size & Age Range	Oral Pathology Evaluated	Main Findings	Risk of Bias
Gang Won Choi et al., 2022 (39)	South Korea	2718 participants	Oral cancer	• Increased risk for oral cavity cancer in patients with MetS. • Higher risk in younger males (<50 years) with ≥ 3 MetS factors.	Low
		20-50 years			
Pallop Siewchaisakul et al., 2020 (40)	Taiwan	17590 participants	Oral potentially malignant disorder (OPMD)	• MetS increased the risk of developing OPMD by 33%. • Components of MetS like central obesity, hypertriglyceridemia, and hyperglycaemia	Low
		30 years and older			

				were significantly associated with OPMD. Central obesity and hypertriglyceridemia specifically linked to leucoplakia.	
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D. Randomized Clinical Trials					
Author & Year	Country	Sample Size & Age Range	Oral Pathology Evaluated	Main Findings	Risk of Bias
Eduardo Montero et al., 2020 (41)	Spain	63 participants Adults (not specified)	Periodontitis and systemic inflammation	- Periodontal treatment notably decreased high sensitivity C-reactive protein (hs-CRP) levels after 6 months. - Major decrease in interleukin-1 beta (IL-1β), TNF-α, hemoglobin A1c (HbA1c), and blood pressure were perceived in the intervention group at 3 months. - Periodontal therapy aids in reducing cardiovascular risk in patients with	Low

				MetS and severe periodontitis.	
Midori Doke et al., 2021 (42)	Japan	112 participants	Effects of dental interventions on MetS	• MetS is associated with visceral fat accumulation and cardiovascular disease. • Dental intervention (prosthesis and periodontal treatment) combined with lifestyle guidance improved metabolic health outcomes, reducing MetS risk.	Low
		Adults (not specified)			

5. DISCUSSION

MetS is a complex disorder characterized by a cluster of metabolic abnormalities, including obesity, hyperglycaemia, hypertension, and dyslipidaemia (1). As research progresses, growing evidence suggests a strong bidirectional relationship between MetS and various oral pathologies (28, 29). The present systematic review synthesizes findings from multiple studies, shedding light on the multi-faceted association between oral pathologies and MetS (29).

5.1. Dental caries and MetS

Dental caries, long understood as a localized microbial disease (11), is now being considered in a broader systemic context, as it has been linked to MetS in several studies. Several studies done worldwide have identified a direct correlation between MetS and an increased risk of dental caries (32, 33).

The case-control study by Ferizi et al. (2022) investigated the association between metabolic control and oral health in children with type 1 diabetes mellitus (T1DM), whereby their oral health was assessed in relation to their metabolic control, measured by glycated haemoglobin (HbA1c) levels (32). The study found that children with poor metabolic control (higher HbA1c levels >7.5%) had significantly higher values of DMFT index, plaque index, and gingival index compared to those with good metabolic control. Additionally, these children exhibited higher counts of cariogenic bacteria, such as *Streptococcus mutans* and *Lactobacillus*, indicating an increased risk for dental caries and periodontal diseases (32).

The mechanisms underlying this association involve several factors. Poor metabolic control in T1DM leads to hyperglycaemia, which can alter salivary composition and reduce its protective functions (5, 6). Although the study reported no significant difference in salivary flow rates between groups, however, the quality of saliva, including its buffering capacity and antimicrobial properties, becomes compromised in poorly controlled diabetic children (5, 6, 32). Henceforth, this environment favours the proliferation of acidogenic and aciduric bacteria, contributing to the development of dental caries (11). Furthermore, chronic hyperglycaemia can impair immune responses, making the oral tissues more susceptible to infections and inflammation, thereby even increasing the risk of periodontal diseases (25, 26).

Furthermore, Iwasaki et al. (2019) offers important insights into the relationship between dental caries and MetS, in which they utilized the DMFT index to assess dental caries (33). Their findings revealed a significant association between higher DMFT scores and the prevalence of MetS, with individuals in the highest quartile of DMFT demonstrating an approximately 80% greater likelihood of having MetS compared to those in the lowest quartile. This association remained significant even after controlling for potential confounding factors, including age, sex, and dietary habits (33).

It is understood that several biological and behavioural mechanisms identified can explain this causal relationship. One major link is the shared dietary risk profile, particularly high intake of free sugars, which not only increases the risk for dental caries but also contributes to obesity, insulin resistance, and dyslipidaemia, all in which are hallmarks of MetS (21, 33). In addition, dental caries, especially when complicated by chronic infection such as pulpitis or periapical periodontitis, may contribute to systemic low-grade inflammation, a central factor in the pathogenesis of MetS, henceforth highlight a bi-directional relationship (25, 26, 33).

Beyond biological mechanisms, the impact of dental caries on nutritional intake may also play a role (33). Advanced caries and tooth loss can impair mastication, leading individuals to avoid hard or fibrous foods such as fruits, vegetables, and whole grains, foods known to protect against MetS. Instead, such individuals may favour soft, processed foods that are significantly higher in sugar and saturated fats, thus exacerbating metabolic risk (11, 33). Collectively, the findings from Iwasaki et al. highlight the potential for dental caries not only to reflect underlying metabolic disturbances but also to actively contribute to their development, reinforcing the need for an integrated approach to oral and systemic health management (28, 29, 33).

Henceforth, the studies by Ferizi et al. (2022) and Iwasaki et al. (2019) collectively reinforce the significant association between dental caries and metabolic disturbances (32, 33). Ferizi et al. showed that children with poorly controlled type 1 diabetes, a condition closely related to MetS, were more prone to caries, due to changes in salivary composition, increased levels of cariogenic bacteria, and impaired immune response (32). Complementing this, Iwasaki et al. demonstrated that higher caries experience, as indicated by DMFT scores, is independently associated with increased MetS prevalence, suggesting shared risk factors such as high sugar intake and chronic inflammation (33). Ultimately, these findings together highlight that dental caries is not only a marker of local oral disease but also an indicator of systemic metabolic imbalance (32, 33).

5.2. Periodontitis and MetS

Periodontitis presents one of the most consistent and well-documented links with MetS (3). Chronic periodontitis has been increasingly identified as both a consequence and a contributing factor to metabolic dysfunction (3, 34, 41).

In a large cross-sectional study by Moradpour et al. (2023) involving 10,000 individuals aged 35–70, a significantly higher prevalence of periodontitis and tooth loss was observed in participants with MetS. The study emphasized systemic inflammation and insulin resistance as shared pathological mechanisms (3).

It was understood that one of the key mechanisms linking periodontitis to MetS is the persistent release of pro-inflammatory cytokines, including interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF- α), and C-reactive protein (CRP), into the systemic circulation (12). These mediators, originating from inflamed periodontal tissues, have been shown to contribute to insulin resistance, impair endothelial function, and promote atherogenesis. Additionally, transient bacteraemia and microbial endotoxemia associated with periodontitis are identified to play a contributory role (3, 12). Periodontal pathogens such as *Porphyromonas gingivalis* can disseminate systemically, activating immune responses via Toll-like receptors (TLRs) and exacerbating metabolic dysfunction. This microbial translocation has also been linked to systemic oxidative stress, which further amplifies insulin resistance and β -cell dysfunction (3).

Furthermore, the study by Moradpour et al. also highlighted the protective effect of daily flossing against MetS (30, 31), reinforcing the importance of oral hygiene practices in systemic disease prevention (3, 30, 31). This finding supports the notion that promoting periodontal health may have far-reaching benefits beyond the oral cavity and bestowing the need for integrated approaches in both dental and medical care settings (3, 13).

Similarly, Kikui et al. (2017) provides compelling evidence of a bidirectional association between MetS and periodontal disease (12, 34). The study found that individuals with MetS had a significantly higher prevalence of periodontal disease, and this risk increased with the number of MetS components present. Individuals with two, three, or four or more components exhibited 1.42, 1.43, and 1.89 fold higher risks, respectively, compared to those without any MetS components (34). Henceforth, associations were drawn between the components of MetS in increasing the risk of an individual to periodontitis (34).

To begin with, high associations were drawn between abdominal obesity periodontal disease (34). The mechanism behind this association is distinguished to be due to the visceral adiposity present in which is a key driver of systemic low-grade chronic inflammation (4). Visceral fat secretes pro-inflammatory adipokines such as TNF- α , IL-6, and resistin, while reducing anti-inflammatory adipokines like adiponectin (4). These cytokines contribute to systemic inflammation that enhances the local inflammatory response in periodontal tissues, promoting gingival inflammation, connective tissue degradation, and alveolar bone loss (4, 34). Additionally, abdominal obesity is strongly linked to insulin resistance (34), which impairs immune function and tissue healing, further exacerbating periodontal breakdown as explained similarly in the study done by Moradpour et al. (2023) clearly highlighting the strong association between hyperglycaemia and periodontitis (3, 12, 34).

Furthermore, this study also showcased an association between hypertension, another key element to MetS and periodontitis (34). Hypertension contributes to vascular endothelial dysfunction and reduced blood flow to the periodontium, impairing the delivery of nutrients and immune cells necessary for maintaining tissue homeostasis and defense (7, 8). Furthermore, increased angiotensin II levels in hypertensive individuals may also stimulate the production of pro-inflammatory mediators and reactive oxygen species (ROS), promoting tissue inflammation and damage (7, 8, 34). Additionally, systemic inflammation common to both hypertension and periodontitis may create a feed-forward loop aggravating both conditions (7, 8, 34).

Additionally, the study done by Kikui et al. (2017) also illustrated that low high-density lipoprotein (HDL) cholesterol levels- dyslipidaemia, was independently associated with an elevated risk of periodontal disease in both men and women (9, 10, 34). This association remained significant even after adjusting for potential confounders such as age and smoking status (34). It is understood that HDL cholesterol exerts multiple protective effects, including anti-inflammatory, antioxidant, and immunomodulatory functions (9). A reduction in HDL levels may impair the resolution of inflammation and enhance the host's susceptibility to chronic

inflammatory conditions such as periodontitis (9, 34). Specifically, HDL modulates the activity of immune cells such as monocytes and macrophages, which play a central role in the innate immune response to periodontal pathogens (10). Dysregulation of these cells in the context of low HDL may result in a sustained pro-inflammatory state and exaggerated immune response, contributing to the destruction of periodontal tissues (9,10, 34). Additionally, HDL is essential for maintaining endothelial function; low HDL levels are associated with endothelial dysfunction, which may impair vascular supply and tissue perfusion in periodontal structures, thereby compromising tissue repair and resistance to infection (9,10). These pathophysiological mechanisms collectively support the hypothesis that low HDL cholesterol not only serves as a biomarker of metabolic dysregulation but also directly contributes to the initiation and progression of periodontal disease (9,10,34).

Henceforth, the studies by Moradpour et al. (2023) and Miki et al. (2017) consistently highlighted a strong association between MetS and periodontal disease (3, 34). Both studies demonstrate that systemic inflammation, insulin resistance, and dysregulated lipid metabolism are key shared mechanisms (25, 26). While Moradpour et al. emphasized the overall prevalence of periodontitis in individuals with MetS (3), Miki et al. detailed how each MetS component, particularly abdominal obesity and low HDL cholesterol contributes to periodontal risk (34). Together, these findings underscore the need for integrated management of oral and metabolic health (3, 13, 34).

5.3. Gingivitis and MetS

Gingivitis, while primarily a local inflammatory response to plaque (14), has been increasingly linked to MetS. Studies show that components of Met, particularly low HDL cholesterol and insulin resistance are associated with a higher risk of gingival inflammation (35, 36).

The study by Kyeong-Soo Lee et al. (2015) explored the association between metabolic syndrome (MetS) parameters and gingivitis in adolescents utilizing data from the Fourth Korea National Health and Nutrition Examination Survey (KNHANES) (35). This cross-sectional analysis revealed that adolescents with an increasing number of MetS components exhibited a higher prevalence of gingivitis (14, 35). Specifically, those with three or more MetS components had an adjusted odds ratio (OR) of 3.29 for developing gingivitis compared to those without MetS components. Among the individual MetS components, low high-density lipoprotein (HDL) cholesterol levels showed a significant independent association with gingivitis, with an adjusted OR of 1.96 (9, 35).

The underlying mechanisms linking MetS to gingivitis are multifaceted (35). Low HDL cholesterol levels are known to impair anti-inflammatory processes and endothelial function, potentially exacerbating inflammatory responses in gingival tissues (9, 10). Additionally, MetS is characterized by systemic low-grade inflammation (25, 26), which can influence periodontal health by promoting pro-inflammatory cytokine production, such as tumour necrosis factor-alpha (TNF- α) and interleukin-6 (IL-6) (4, 35). These cytokines may mediate the association between MetS and periodontal diseases, including gingivitis (35).

Additionally, the study by K. Ka et al (2017), examined the association between MetS and gingival inflammation in obese children aged 8–10 years (36). The researchers focused on measuring levels of tumor necrosis factor-alpha (TNF- α) in gingival crevicular fluid (GCF), a biomarker indicative of periodontal inflammation (25, 26). Their findings revealed that among obese boys, those diagnosed with MetS exhibited significantly higher GCF TNF- α concentrations, approximately 44.9% greater compared to their counterparts without MetS (36). Interestingly, this association was not observed in obese girls, suggesting potential sex-specific differences in the relationship between MetS and gingival inflammation (25, 36).

The mechanisms underlying this association involve systemic inflammation and immune dysregulation (9,10). MetS is characterized by chronic low-grade inflammation, which can exacerbate inflammatory responses in the gingival tissues, leading to gingivitis (14). Additionally, components of MetS, such as dyslipidaemia and insulin resistance, may impair host immune responses, making the gingival tissues more susceptible to bacterial plaque accumulation and subsequent inflammation (25, 26, 14). The strong association between low HDL cholesterol and gingivitis suggests that lipid metabolism plays a role in periodontal health, potentially through its effects on inflammatory pathways and endothelial function (9, 36).

Both Kyeong-Soo Lee et al. (2015) and K. Ka et al. (2017) demonstrate a clear association between gingivitis and MetS. Lee et al. showed that adolescents with more MetS components had higher rates of gingival inflammation, especially with low HDL levels (35). Ka et al. supported this by identifying increased TNF- α levels in the gums of obese boys with MetS, linking systemic inflammation to gingival disease (36). These findings suggest that MetS contributes to gingival inflammation through shared inflammatory pathways, reinforcing the importance of early, integrated care for metabolic and oral health (25, 26, 35, 36).

5.4. Xerostomia and MetS

Xerostomia, or dry mouth, has been increasingly linked to MetS, whereby the association may be driven by systemic inflammation, autonomic dysfunction, and metabolic changes affecting salivary gland function (16, 17). As such, xerostomia may serve as a potential oral manifestation or early indicator of underlying metabolic imbalance, as their association is relevant and this has been showcased in several studies (37, 38).

The study by González et al. (2021) explored the association between xerostomia and MetS in adults, in which xerostomia was significantly more frequent in women and increased with age (37). Furthermore, it was found for xerostomia to be associated with several systemic diseases, including diabetes mellitus, hypertension, and obesity, as well as oral functional disorders such as tooth mobility (37).

The mechanisms underlying this association may involve systemic inflammation, autonomic dysfunction, and metabolic disturbances. MetS is characterized by chronic low-grade inflammation, consequently leading to elevated pro-inflammatory cytokines such as IL-6 and TNF- α , which can impair salivary gland function and reduce salivary flow (25, 26, 16). Additionally, components of MetS, such as insulin resistance and dyslipidaemia which are commonly faced by obese people, may affect the autonomic nervous system, leading to decreased parasympathetic stimulation of salivary glands and further contributing to xerostomia (5, 9, 16). Additionally, dyslipidaemia, is discerned to negatively affect the vascular supply to the salivary glands, further reducing salivary secretion (9, 16). Furthermore, medications used to manage MetS, such as antihypertensives and antidiabetic drugs, can have side effects that reduce salivation, further exacerbating the oral pathology (17).

Conversely, González et al. (2021) highlighted a bi-directional relationship between MetS, and xerostomia. This means that not only does MetS and obesity increase the risk of developing dry mouth, but having dry mouth itself may exacerbate or even contribute to the progression of MetS (37). The study illustrated how xerostomia can negatively impact oral health, leading to difficulties in chewing, swallowing, and speaking, as well as an increased risk of dental caries and periodontal disease (28). Ultimately, this exacerbates the overall health burden of MetS (29), as poor oral health has been linked to systemic inflammation, insulin resistance, and cardiovascular disease, which are core components of MetS (1, 29, 37). In this way, xerostomia can act as both an early warning sign of metabolic disturbances and a contributing factor to the progression of MetS, creating a complex feedback loop (37).

Additionally, this association was further illustrated through the study done by Khongsirisombat et al. (2021) which showcased that individuals diagnosed with MetS reported higher levels of oral dryness (38). The research revealed that obesity, a key component of MetS, was particularly linked to increased oral dryness and negatively impacted oral health-related quality of life (OH-QoL) (4, 16, 38). The mechanisms behind this association involve several factors such as systemic inflammation and autonomic dysfunction which were explained previously (9, 16). Furthermore, this study illustrated that obesity-related metabolic disturbances may exacerbate oral dryness through increased inflammatory markers and altered metabolic processes that further impair salivary function (29, 38).

Both Alba Pérez-González et al. (2021) and Khongsirisombat et al. (2021) demonstrated a significant bi-directional relationship between xerostomia and MetS (37, 38). MetS contributes to xerostomia through chronic inflammation, autonomic dysfunction, and metabolic disturbances that impair salivary gland function (28). In turn, xerostomia negatively impacts oral health, potentially exacerbating systemic inflammation and metabolic imbalance (29) underscores the importance of integrated management of both oral and metabolic health (3, 37, 38).

5.5. Oral cancer and MetS

Oral cancer, primarily oral squamous cell carcinoma, arises in the tissues of the mouth and is influenced by factors like tobacco, alcohol, and HPV (18). Recent evidence links MetS to increased oral cancer risk through chronic inflammation, oxidative stress, and hormonal imbalances that promote cancer cell growth and survival (18, 39, 40).

The study by Gang Won Choi et al. (2022) investigated the association between MetS and the risk of oral cavity cancer, utilizing data from the Korean National Health Insurance Service (39). The findings revealed that individuals with MetS had a significantly higher risk of developing oral cavity cancer, particularly among males. Specifically, the hazard ratio (HR) for oral cavity cancer in patients with MetS was 1.113, with a more pronounced risk observed in males (39). Furthermore, the risk increased with the number of MetS components present; individuals with three or more MetS factors had an HR of 1.191, and this risk was notably higher in males under 50 years of age, with an HR of 1.439 (39).

The study investigated several mechanisms through which MetS may increase the risk of oral cancer (39). One key pathway is chronic systemic inflammation, where excess adipose tissue in MetS promotes the release of pro-inflammatory cytokines like IL-6, TNF- α , and CRP, which

can damage DNA and support malignant transformation (18, 25, 26). Additionally, insulin resistance and resulting hyperinsulinemia elevate levels of insulin-like growth factor-1 (IGF-1), a hormone that stimulates cell proliferation and inhibits apoptosis, creating conditions favourable for tumour growth (5, 6, 18). Oxidative stress, another hallmark of MetS, further contributes to DNA damage and disrupts cellular repair mechanisms (18). Dyslipidaemia, marked by high triglycerides and low HDL cholesterol, can lead to lipid peroxidation and membrane instability, aiding carcinogenesis (9, 10). Finally, immune dysfunction in MetS may impair the body's ability to detect and destroy abnormal cells, allowing precancerous changes in oral tissues to progress unchecked (25, 26, 18). Collectively, these mechanisms suggest a biological basis for the observed association between MetS and increased oral cancer risk, particularly in males and younger populations (39).

Furthermore, the study by Siewchaisakul et al. (2020) also provided robust evidence for the association between MetS and the development of oral potentially malignant disorders (OPMDs), which are known precursors to oral cancer (40). This study showcased that individuals with MetS had a 33% higher risk of developing OPMDs compared to those without MetS, with an adjusted rate ratio (aRR) of 1.33 and a 95% confidence interval (CI) of 1.14–1.55. This means the observed association is statistically significant, as the entire CI lies above 1, indicating a true increased risk rather than a chance finding (40). When examining individual MetS components, the study found that central obesity was associated with a 22% increased risk (aRR = 1.22; 95% CI: 1.03–1.44), hypertriglyceridemia with a 26% increased risk (aRR = 1.26; 95% CI: 1.08–1.47), and hyperglycaemia with a 20% increased risk (aRR = 1.20; 95% CI: 1.03–1.41), all of which were statistically significant due to their confidence intervals excluding the null value of 1 (40). Importantly, central obesity (4) and hypertriglyceridemia (9,10) were specifically linked to oral leucoplakia, a common and clinically relevant subtype of OPMDs (18). These findings suggest that metabolic dysregulation plays a crucial role in oral epithelial transformation (25, 26, 18). This is due to several mechanisms including chronic low-grade inflammation, oxidative stress, and insulin resistance, which together contribute to DNA damage, disruption of normal cell turnover, and impaired immune surveillance in oral tissues as mentioned previously (25, 26, 40).

The studies by Gang Won Choi et al. (2022) and Siewchaisakul et al. (2020) highlight a clear association between MetS and increased risk of oral cancer and its precursors (39, 40). MetS components, particularly obesity, hyperglycaemia, and dyslipidaemia were linked to both oral cancer and OPMDs (39, 40). The underlying mechanisms involve chronic inflammation, oxidative stress, and insulin resistance, which contribute to cellular damage and cancer

development (25, 26, 29). These findings emphasize the importance of managing MetS to reduce oral cancer risk (30, 31, 40).

5.6. The role of dental interventions in MetS management

Dental interventions have shown increasing promise in the management of MetS, with studies highlighting their role in reducing systemic inflammation, improving metabolic health, and enhancing overall outcomes (41, 42).

The research by Eduardo Montero et al. (2020) investigated the impact of intensive periodontal treatment on patients with MetS and severe periodontitis (41). The randomized controlled trial found that after undergoing periodontal therapy, patients experienced a significant reduction in systemic inflammation, as evidenced by a marked decrease in high-sensitivity C-reactive protein (hs-CRP) levels, a well-known marker for systemic inflammation associated with MetS, particularly cardiovascular risk (25, 26, 41). This ultimately, resulted in improved glycaemic control (HbA1c), and lowered blood pressure, demonstrating that periodontal therapy may offer systemic metabolic benefits (31, 41). Furthermore, the study suggested that periodontal treatment could be a crucial tool in managing MetS, particularly for individuals with severe oral disease (41). These findings underscore the potential of periodontal therapy to mitigate the systemic effects of MetS, which could lead to better overall health outcomes (31, 41).

Similarly, the study by Midori Doke et al. (2021) expanded on the role of dental interventions by combining prosthodontics, periodontal treatment, and lifestyle modifications (such as diet and exercise) to manage MetS in a randomized controlled trial (42). The research found that participants who received dental treatments alongside lifestyle changes showed substantial improvements in anthropometric measures, including waist circumference and body mass index (BMI), which are key indicators of MetS (4, 30, 42). Additionally, these participants had improved blood pressure and lipid profiles, both of which are integral components of MetS (1, 42). This study suggests that dental interventions, when combined with lifestyle counseling, can contribute significantly to reducing the risk of MetS and improving both metabolic and oral health (30, 42). The findings emphasize that oral health is not only important for local health but can also play a pivotal role in systemic conditions like MetS and vice versa (31, 42).

Ultimately, the bi-directional relationship between MetS and oral health reveals that MetS can worsen oral diseases like periodontitis (28, 3), while chronic oral conditions can exacerbate

MetS by increasing systemic inflammation (29, 34). Studies by Montero et al. (2020) and Doke et al. (2021) highlight the benefits of oral interventions in managing MetS, showing that improving oral health can positively impact metabolic factors such as insulin resistance and blood pressure (41, 42). This interconnection emphasizes the importance of integrating oral care into MetS management for better overall health outcomes both orally and metabolically alongside positive lifestyle changes (30, 31, 41, 42).

6. CONCLUSION

The primary goal of this research study was to investigate literature reviews to assess whether MetS contributes to an increased risk of developing oral pathologies and vice versa. Consequently, the investigation into existing literature revealed a significant bidirectional relationship between MetS and oral pathologies. It was understood that numerous studies supported the notion that the systemic inflammation and insulin resistance characteristic of MetS contributes to the onset and progression of oral diseases, particularly periodontitis. Conversely, chronic oral infections, especially periodontal disease, may exacerbate systemic inflammation, potentially playing a role in the development or worsening of metabolic syndrome. This interplay suggests a mutually reinforcing relationship that warrants attention in both medical and dental fields.

In relation to the secondary objective, it was analysed that the individual components of metabolic syndrome such as obesity, hyperglycaemia, hypertension and dyslipidaemia demonstrated a clear association between them various oral health issues. For instance, obesity has been associated with increased oral inflammation and dental caries, whilst hyperglycaemia is strongly linked to increased risk of periodontal disease due to impaired immune function and delayed wound healing. Additionally, hypertension and altered lipid profiles may contribute to periodontal tissue breakdown promoting oral tissue degradation, whilst altering salivary composition and its buffer capacity. These findings highlight the importance of considering the full spectrum of MetS components when assessing oral health risks.

The literature also showcased that improved management of metabolic syndrome can have a positive impact on oral health, and vice versa. Lifestyle modifications such as diet, exercise, and smoking and alcohol cessation, alongside pharmacological interventions, have shown potential in reducing both systemic inflammation and periodontal disease severity. Likewise, effective periodontal therapy may help lower systemic inflammatory markers and improve glycaemic control in individuals with MetS. Therefore, integrating dental care with metabolic health management could offer a more integrated approach to reducing the burden of both conditions.

7. SUSTAINABILITY

Based on the results obtained, the association between oral pathologies and MetS presents several opportunities for sustainable healthcare strategies.

Economically, early recognition and joint management of these interconnected conditions can reduce the financial burden on both patients and healthcare systems. Preventive approaches targeting shared risk factors such as poor diet, smoking and obesity can help avoid costly interventions like periodontal surgeries or advanced metabolic treatments such as cardiac surgery.

Environmentally, integrating non-invasive diagnostic methods such as salivary biomarkers for inflammation or glycaemic control, whilst reducing over-reliance on pharmaceutical and surgical treatments lowers clinical waste (repeated blood tests) and energy consumption (radiographic imaging). Encouraging lifestyle-based interventions contributes to a more eco-conscious model of care.

Socially, the findings highlight the importance of accessible, interdisciplinary healthcare. Public health initiatives that address both oral hygiene and metabolic health, especially in vulnerable populations can promote long-term wellbeing and reduce health disparities. Aligning care with preventive, patient-centred and collaborative principles enhances sustainability in both dental and medical fields.

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9. ANNEXES

A. Annex 1: Abbreviations *(arranged in alphabetical order)*

- 1) Adjusted rate ratio: aRR
- 2) CDC: Centres for Disease Control and Prevention
- 3) CHD: Coronary heart disease
- 4) CRP: C-reactive protein
- 5) CVD: Cardiovascular diseases
- 6) DBP: Diastolic blood pressure
- 7) DMFT: Decayed, missing, filled, teeth
- 8) GCF: Gingival crevicular fluid
- 9) HbA1c: Hemoglobin A1c
- 10) HDL: High-density lipoprotein
- 11) hs-CRP: High sensitivity C-reactive protein
- 12) IARC: International Agency for Research on Cancer
- 13) IDL: Intermediate-density lipoprotein
- 14) IL-1 β : interleukin-1 beta
- 15) NIH: National Institutes of Health
- 16) OH-QoL: Oral-health related quality of life
- 17) OPMD: Oral potentially malignant disorder
- 18) OSCC: Oral squamous cell carcinoma
- 19) RAAS: Renin-angiotensin-aldosterone system
- 20) SBP: Systolic blood pressure
- 21) T1DM: Type 1 diabetes mellitus
- 22) TNF- α : Tumour necrosis factor-alpha
- 23) VLDL: Very-low-density lipoprotein
- 24) WC: Waist circumference
- 25) WHO: World Health Organization

B. Annex 2: Search Strategy

Database	Search Query	Filters Applies	Search Date
UEM CRAI library	"Metabolic syndrome" AND "oral health"	- 2015-2025 - Peer-reviewed - Full-text articles - English/Spanish	- October 2024 - March 2025
PubMed	"Metabolic syndrome" OR "obesity" OR "hyperglycemia" OR "hypertension" OR "dyslipidemia") AND ("dental caries" OR "periodontitis" OR "gingivitis" OR "xerostomia" OR "oral tumors"		
Google Scholar	"Metabolic syndrome" AND "oral health" OR "oral pathologies"		
Medline Plus	"Metabolic syndrome" AND "oral diseases"		

C. Annex 3: Newcastle-Ottawa Scale

- **Assessment form for case-control studies**

Newcastle-Ottawa Quality Assessment Form for Case-Control Studies

Note: A study can be given a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Reviewer: _____

Ref ID: _____

Selection

- 1) Is the case definition adequate?: _____
 - a) Yes, with independent validation **(one star)**
 - b) Yes, e.g., record linkage or based on self report
 - c) No description
- 2) Representativeness of the cases: _____
 - a) Consecutive or obviously representative series of cases **(one star)**
 - b) Potential for selection biases or not stated
- 3) Selection of controls: _____
 - a) Community controls **(one star)**
 - b) Hospital controls
 - c) No description
- 4) Definition of controls: _____
 - a) No history of disease (endpoint) **(one star)**
 - b) No description of source

Comparability

- 1) Comparability of cases and controls on the basis of the design or analysis controlled for confounders:
☐ The study controls for age **(one star)**
☐ Study controls for other factors (list) _____ **(one star)**
☐ Cohorts are not comparable on the basis of the design or analysis controlled for confounders

Exposure

- 1) Ascertainment of exposure: _____
 - a) Secure record (e.g., surgical record) **(one star)**
 - b) Structured interview where blind to case/control status **(one star)**
 - c) Interview not blinded to case/control status
 - d) Written self report or medical record only
 - e) No description
- 2) Same method of ascertainment for cases and controls: _____
☐ Yes **(one star)**
☐ No
- 3) Non-response rate: _____
 - a) Same rate for both groups **(one star)**
 - b) Non-respondents described
 - c) Rate different between cases and controls with no description

Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa: Ottawa Hospital Research Institute. https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.

- **Assessment form for cross-sectional studies**

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE

(adapted for cross sectional studies)

Selection: (Maximum 5 scores)

1) Representativeness of the cases:

- a) Truly representative of the HCC patients (consecutive or random sampling of cases). 1 score
- b) Somewhat representative of the average in the HCC patients (non-random sampling). 1 score
- c) Selected demographic group of users. 0 score
- d) No description of the sampling strategy. 0 score

2) Sample size:

- a) Justified and satisfactory (≥ 400 HCC included). 1 score
- b) Not justified (<400 HCC patients included). 0 score

3) Non-Response rate

- a) The response rate is satisfactory ($\geq 95\%$). 1 Score
- b) The response rate is unsatisfactory ($<95\%$), or no description. 0 Score

4) Ascertainment of the screening/surveillance tool:

- a) Validated screening/surveillance tool. 2 scores
- b) Non-validated screening/surveillance tool, but the tool is available or described. 1 score
- c) No description of the measurement tool. 0 score

Comparability: (Maximum 1 stars)

1) The potential confounders were investigated by subgroup analysis or multivariable analysis.

- a) The study investigates potential confounders. 1 score
- b) The study does not investigate potential confounders. 0 score

Outcome: (Maximum 3 stars)

1) Assessment of the outcome:

- a) Independent blind assessment. 2 scores
- b) Record linkage. 2 scores
- c) Self report. 1 score

- d) No description. 0 score

2) Statistical test:

- a) The statistical test used to analyze the data is clearly described and appropriate. 1 score
- b) The statistical test is not appropriate, not described or incomplete. 0 score

Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa: Ottawa Hospital Research Institute. https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.

- **Assessment form for cohort studies**

Newcastle-Ottawa Quality Assessment Form for Cohort Studies

Note: A study can be given a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

Selection

- 1) Representativeness of the exposed cohort
 - a) Truly representative (*one star*)
 - b) Somewhat representative (*one star*)
 - c) Selected group
 - d) No description of the derivation of the cohort
- 2) Selection of the non-exposed cohort
 - a) Drawn from the same community as the exposed cohort (*one star*)
 - b) Drawn from a different source
 - c) No description of the derivation of the non exposed cohort
- 3) Ascertainment of exposure
 - a) Secure record (e.g., surgical record) (*one star*)
 - b) Structured interview (*one star*)
 - c) Written self report
 - d) No description
 - e) Other
- 4) Demonstration that outcome of interest was not present at start of study
 - a) Yes (*one star*)
 - b) No

Comparability

- 1) Comparability of cohorts on the basis of the design or analysis controlled for confounders
 - a) The study controls for age, sex and marital status (*one star*)
 - b) Study controls for other factors (list) _____ (*one star*)
 - c) Cohorts are not comparable on the basis of the design or analysis controlled for confounders

Outcome

- 1) Assessment of outcome
 - a) Independent blind assessment (*one star*)
 - b) Record linkage (*one star*)
 - c) Self report
 - d) No description
 - e) Other
- 2) Was follow-up long enough for outcomes to occur
 - a) Yes (*one star*)
 - b) No

Indicate the median duration of follow-up and a brief rationale for the assessment above: _____

- 3) Adequacy of follow-up of cohorts
 - a) Complete follow up- all subject accounted for (*one star*)
 - b) Subjects lost to follow up unlikely to introduce bias- number lost less than or equal to 20% or description of those lost suggested no different from those followed. (*one star*)
 - c) Follow up rate less than 80% and no description of those lost
 - d) No statement

Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa: Ottawa Hospital Research Institute. https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.

- **Assessment form for randomized clinical trial**

- 1) Cochrane risk-of-bias tool



Chapter 8: Assessing risk of bias in a randomized trial

Julian PT Higgins, Jelena Savović, Matthew J Page, Roy G Elbers, Jonathan AC Sterne

Key Points:

- This chapter details version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2), the recommended tool for use in Cochrane Reviews.
- RoB 2 is structured into a fixed set of domains of bias, focusing on different aspects of trial design, conduct and reporting.
- Each assessment using the RoB 2 tool focuses on a specific result from a randomized trial.
- Within each domain, a series of questions ('signalling questions') aim to elicit information about features of the trial that are relevant to risk of bias.
- A judgement about the risk of bias arising from each domain is proposed by an algorithm, based on answers to the signalling questions. Judgements can be 'Low', or 'High' risk of bias, or can express 'Some concerns'.
- Answers to signalling questions and judgements about risk of bias should be supported by written justifications.
- The overall risk of bias for the result is the least favourable assessment across the domains of bias. Both the proposed domain-level and overall risk-of-bias judgements can be overridden by the review authors, with justification.

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