GRADUATION PROJECT

Degree in Dentistry

TYPE 2 DIABETES MELLITUS AND PERIODONTAL DISEASE

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SUMMARY

Introduction: Type 2 diabetes mellitus (T2DM) and periodontal disease are chronic, interrelated conditions that share inflammatory and metabolic pathways. Their intertwined relationship has growing implications for both dental and medical healthcare. **Objectives:** This study aimed to investigate the bidirectional relationship between T2DM and periodontal disease, focusing on three key areas: epidemiology, pathophysiological mechanisms, and clinical management. **Methods:** A literature review was conducted using databases such as PubMed, Google Scholar, and the CRAI Dulce Chacón library to find recent and relevant peer-reviewed scientific articles, as well as clinical trials, cross- sectional studies and cohort studies for the analysis of the results. **Results:** The findings were studied across three thematic axes to explore how each condition influences the other and to identify association between the conditions and evidence-based interventions to slow down their progression. **Conclusions:** Findings confirm that T2DM is associated with an increased prevalence and severity of periodontitis, while periodontitis may also elevate the risk of developing T2DM. Shared mechanisms between both conditions include systemic inflammation, oxidative stress, and impaired healing. Non-surgical periodontal therapy (NSPT) improves both periodontal health and glycemic control, and adjunctive therapies such biomarkers for inflammation monitoring, Host modulation therapies and pharmacological agents also show promise. T2DM and periodontal disease are closely linked through biological and clinical pathways so increasing social awareness and integrating periodontal care into diabetes management with a collaboration between dental and medical healthcare professionals can enhance outcomes and improve the management of patients affected by both conditions.

KEYWORDS

Dentistry, Type 2 Diabetes Mellitus (T2DM), Periodontal Disease.

RESUMEN

Introducción: La diabetes mellitus tipo 2 (DM2) y la enfermedad periodontal son enfermedades crónicas interrelacionadas que comparten vías inflamatorias y metabólicas. Esta relación bidireccional tiene implicaciones relevantes tanto para la atención médica como odontológica. **Objetivos:** Investigar la relación bidireccional entre DM2 y la enfermedad periodontal, enfocándose en epidemiología, mecanismos fisiopatológicos y manejo clínico. **Métodos:** Se realizó una revisión bibliográfica en bases como PubMed, Google Scholar y la biblioteca CRAI Dulce Chacón, seleccionando artículos científicos recientes, revisados por pares, incluyendo ensayos clínicos, estudios transversales y de cohortes. **Resultados:** Se analizaron los hallazgos en tres ejes temáticos para comprender cómo cada condición influye en la otra e identificar intervenciones basadas en evidencia que pueden frenar su progresión. **Conclusiones:** Los estudios confirman que la DM2 se asocia con mayor prevalencia y gravedad de periodontitis, mientras que esta puede incrementar el riesgo de desarrollar DM2. Ambas patologías comparten mecanismos como inflamación sistémica, estrés oxidativo y cicatrización deficiente. La terapia periodontal no quirúrgica (TPNQ) mejora la salud periodontal y el control glucémico. Además, terapias complementarias como biomarcadores inflamatorios, moduladores del huésped y agentes farmacológicos muestran resultados prometedores. Dado el vínculo biológico y clínico entre DM2 y enfermedad periodontal, es crucial aumentar la conciencia social e integrar el cuidado periodontal en el manejo de la diabetes mediante la colaboración entre profesionales médicos y odontológicos para mejorar los resultados en pacientes afectados por ambas condiciones.

PALABRAS CLAVE

Odontología, Diabetes Mellitus Tipo 2 (DMT2), Enfermedad Periodontal.

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1. INTRODUCTION

1.1. Overview of diabetes mellitus

Diabetes Mellitus: more often known as diabetes, is a complex metabolic disease that is distinguished by an elevated level of glucose in the blood or hyperglycemia as a cause of defective insulin activity or secretion over an extended period of time (1). This disease encompasses three main types of diabetes including type 1 diabetes, or early onset diabetes (2). It is characterized by a cell-mediated autoimmune dismantling of the cells that produce insulin, known as the beta cells of the islets of Langerhans present in the pancreas, therefore resulting in hyperglycemia due to insulin deficiency (2). The second one, type 2 diabetes, also the most frequent form of the disease, is marked by hyperglycemia due to insufficient action of insulin, secretion, or both at the same time (3). This phenomenon could eventually lead to a loss of insulin production on the long term. The third type is gestational diabetes, and as its' name indicates, it occurs during pregnancy as an impaired tolerance of glucose in women carrying a baby (4) and eventually resolves after the birth of the child.

1.1.1 A deeper look into type 2 diabetes mellitus

Type 2 diabetes mellitus (T2DM) comprises more than 90% of recorded cases of diabetes around the world (2) . This staggering figure as well as the incidence of the disease which is in a constant rise is alarming and arouses the curiosity of researchers all around the world (1).
Fasting and postprandial hyperglycemia due to insulin resistance are the main markers of T2DM and are the key contributors to the emergence of various life-threatening complications (1). Insulin resistance is when fat, muscle and liver cells in the body resist the effect of insulin, making hard for glucose to enter the cells effectively to be stored as energy, therefore increasing the blood sugar levels (5). Over time, this could lead to an impairment of insulin secretion as the organ producing insulin, the pancreas, is unable to deal with this resistance and to compensate for the lack of insulin, which in turn causes even higher blood glucose levels (5).

1.1.2 Diagnosis of the disease

With a complex and heterogeneous etiology, this disease has a slow onset and with symptoms that could fester for a long time without being noticed (1,3). The classic symptoms of diabetes often include the "three Ps": increased appetite (polyphagia), excessive thirst (polydipsia), and frequent urination (polyuria). Others consist of fatigue, blurred vision, and sudden weight loss.

To diagnose T2DM there are two key measures, the first one being the glycated hemoglobin levels, also known as HbA1c, which is a measure of the blood glucose levels over a period or two to three months (6). In the blood, there are different types of cells, notably red blood cells amongst others. These cells possess a protein known as hemoglobin, responsible for transporting oxygen throughout the bloodstream. lucose in the blood, it binds to hemoglobin, therefore HbA1c reflects the long-term quantities of glucose in the blood (6). HbA1c values between 5.7% and 6.4% indicate a person that is prediabetic, anything below that is considered to be normal. However, values of 6.5% or higher signifies the patient is diabetic (6). The second key measure for diagnosing diabetes is the fasting blood glucose levels, which is measured after at least 8 hours without eating, and it permits us to have a more immediate result of blood glucose levels, compared to the HbA1c levels. It could be useful in cases where the latter is affected by conditions that impact red blood cell turnover, for example anemia (7). We can diagnose T2DM with a repeated value of 7.0 mmol/L (126 mg/dL) for the fasting blood glucose. Both these measures allow us to have a long-term or immediate view of glucose regulation in a patient.

Test	**Normal**	**Prediabetes**	**Diabetes**
HbA1c	< 5.7%	5.7% to 6.4%	> 6.5%
Fasting blood glucose	< 100 mg/dL	100 to 125 mg/dL	> 126 mg/dL

Table 1. Values used to diagnose diabetes (6,7)

In addition to the values of HbA1c and fasting blood, there are other ways to diagnose T2DM. In individuals who exhibit symptoms of hyperglycemia such as increased thirst and urination, if they exhibit a random plasma glucose level of 200 mg/dL (11.1 mmol/L) or above, it can also indicate diabetes type 2 (8). Another accurate measurement of blood glucose levels is the Oral Glucose Tolerance Test (OGTT) which is another frequently used diagnostic method. This test is a measurement of the levels of blood sugar 2 hours after ingesting a solution that is glucose rich. Prediabetes is indicated by values between 140 and 199 mg/dL and diabetes is

diagnosed by an OGTT result of 200 mg/dL or above (6,8). The use of these supplementary diagnostic techniques offers useful resources to diagnose diabetes when HbA1c or fasting blood glucose results are unclear.

1.1.3 The epidemiology of the disease

Type 2 diabetes mellitus has emerged as a significant global health issue, as we have seen in the recent decades, it's prevalence skyrocketing. From about 108 million people affected worldwide in 1980, the prevalence of T2DM has escalated to epidemic proportions with over 400 million people who are estimated to be affected by the disease globally (1), and it is believed that by 2045, this number is expected to increase to 700 million people (2,9). This increase by fourfold of the number is mostly explained by the changes in lifestyle, the aging of populations, and the staggering rise in obesity rates.

Affecting over 10% of the overall adult population in the world, we notice that over half of these individuals are above the age of 65 (10,11). It is observed that in high income countries, the rates of T2DM are more elevated, compared to middle and low socioeconomic groups where the trend show a disproportionate impact, however, with a notable increase in the past few years which could be due to the lack of infrastructure that could be needed to effectively control this epidemic (10). Other differences in the epidemiology of T2DM, on a regional and demographic level could be influenced by factors like genetic predispositions, lifestyle and environmental variables (12).

1.1.4. Pathophysiology of Type 2 diabetes mellitus

Presenting complicated and varied etiology, the main cause of T2DM is Impaired insulin sensitivity and pancreatic beta-cell dysfunction, with the pancreas being the organ responsible for the production of insulin (5). When the insulin-sensitive tissues in the body, particularly the liver, the muscles and the adipose tissues do not recognize or react to insulin present, this will result in a decrease in the absorption of glucose and an elevation in the production of hepatic glucose, which is the phenomenon known as insulin resistance (13). Chronic inflammation and metabolic abnormalities frequently associated with obesity exacerbate this process by the stimulation of production of inflammatory cytokines and free fatty acids (13).

A key consequence of chronic inflammation is heightened insulin resistance, as it hinders glucose from efficiently entering body tissues and being stored as energy. In the meantime, the pancreas tries to compensate for this resistance by trying to produce more insulin before failing on the long-term as a result of ongoing metabolic stress on the organism (5,13).

Beta-cell dysfunction or even mortality, is frequently linked to amyloid deposition and buildup in the islets on Langerhans, which could lead to the modification of the compositions of cells in the islets such as an elevation in the alpha-cell volume in some people (5). The increase in alpha-cells, which are the cells responsible for the production of glucagon, the antagonistic hormone to insulin in the regulation of blood glucose levels, will in turn stimulate glucose production therefore elevating the blood glucose levels even more. This glucagon excess further impedes blood sugar control, creating a feedback loop that worsens metabolic imbalance in these patients (5,12). These mechanisms contribute to the exacerbation of chronic hyperglycemia in patients with T2DM.

1.1.5. Complications of the disease

Diabetes in itself poses a huge global health threat, moreover it is also known to induce some serious complications.

Complications could be acute, also called diabetic emergencies, like a hyperglycemic crisis which leads to diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS)(2,12). Although much more frequent in type 1 diabetes mellitus, DKA happens when there is a complete depletion of insulin, so the body has to tap into the stored body fat for energy (14). Characterized by the low pH it induces due to the high ketoacid levels, this condition could be life-threatening. Hyperglycemic hyperosmolar state is predominantly seen in type 2 diabetic adults and occurs when a state of maintained hyperglycemia and dehydration of the body lead to an altered mental state such as confusion, lethargy or even coma (14). The hyperglycemic values exceed 600 mg/dL and show high plasma osmolality (over 320 mOsm/kg) without the production of ketone bodies (14). Due to delayed diagnosis and often people presenting other coexisting conditions, HHS presents a high mortality rate (14).

Furthermore, complications could be chronic; as time passes, a persistent hyperglycemia can lead to damaged blood vessels and organs. There are two main categories for the classification of T2DM complications: microvascular and macrovascular complications (2).

People with long term diabetes have been shown to display microvascular complications, or issues with the small blood vessels in the body. These complications include nephropathy, neuropathy, and retinopathy. Prolonged high blood sugar levels lead to kidney damage and frequently manifests as a decrease in glomerular filtration rates and albuminuria. This condition is called diabetic nephropathy, and it constitutes globally the primary cause of end-stage renal

disease (2,3). Diabetic neuropathy affects the small vessels in the nervous system, notably the peripheral nervous system, which causes an impairment in the nervous signaling to the extremities of the body, such as the hands and feet. This condition could cause numbness or even pain, and in extreme cases could induce ulcers leading to the amputation of the feet, also known as diabetic foot, it is a leading reason of morbidity and significantly affects patients' quality of life. (15). As for the third main microvascular complication, diabetic retinopathy occurs due to the very elevated blood glucose levels, that damages the blood vessels in the retina, making them swell and leak and causing vision impairment and in some cases blindness. This condition usually affects both eyes and is considered that in adults worldwide, diabetic retinopathy is the leading cause of blindness (15).

Another type of complications are the macrovascular complications which are the ones affecting the large blood vessels in patients with T2DM. Cardiovascular diseases like coronary artery disease, strokes, and peripheral artery disease are the main types of macrovascular complications, and they are major causes of morbidity and mortality in affected patients (2). Accelerated atherosclerosis, which is when there is plaque build-up in the walls of the arteries, leading them to thicken and harden is what mainly leads to these complications (2). People with constant elevated blood glucose levels causing insulin resistance, develop metabolic imbalances which lead to endothelial dysfunction which exacerbates this process. Coronary artery disease, a condition where the blood supply to the heart is limited can result in myocardial infraction or even a heart attack. Another serious consequence could be a decrease of blood supply to the brain as a result of an artery that has been clogged or that has burst. Finally, Peripheral artery disease leads to complications in vessels that run outside the heart and the brain, mainly those feeding the lower limbs, and leading to impaired movement and the need for amputation in some serious cases (2).

Research shows that individuals with type 2 diabetes have an increased likelihood of developing cardiovascular disease. This probability is increased by fourfold compared to people without the disease, which shows the importance of controlling the disease blood glucose levels in order to avoid the development of such complications (2,15).

By covering the most talked about complications in the diabetes world, we sometimes fail to recall that diabetes also impacts other things in our body and most notably the mouth and teeth. In fact, there are some oral pathologies that are frequently present in diabetic patients. Of these pathologies, we find xerostomia, commonly referred to dry mouth condition which is caused by reduced saliva production and altered composition (16). Burning mouth syndrome

and taste alterations (dysgeusia) can also be noted. Additionally oral infections such as periapical lesions, oral candidiasis, angular cheilitis, and prosthetic stomatitis are very prevalent (16) and conditions like oral lichen planus and glossitis (fissured tongue) also appear also in a higher percentage than in non-diabetic patients. This can be explained by the uncontrolled elevation of blood glucose, which delays wound healing significantly, especially following traumatic ulcers from dental prostheses and post-surgical dental procedures (17).

However, central to our focus is the staggering increase in periodontal disease which is a less discussed complications of diabetes but is very closely linked to systemic health complications (17).

1.2 An overview of periodontal disease

Periodontal disease, composed of gingivitis and periodontitis, is a long-term inflammatory condition affecting the structures that support the teeth, involving the gums, periodontal ligament, and alveolar bone. (18). The process starts with the accumulation of bacteria in the mouth that forms a bacterial biofilm and creates dental plaque which disrupts the equilibrium of the oral microbiome and triggers an immunological response. If untreated, this response results in tissue and bone destruction around the teeth (19).

The constant and progressive damage that is done to the tissues surrounding teeth is displayed as inflammation to the gums, and bleeding of the gums, and the formation of periodontal pockets between the tooth and supporting tissues. This phenomenon could eventually lead to tooth loss (20). In addition to having localized effects, periodontal disease has systemic implications on the overall health of the patient as pathogenic bacteria and inflammatory mediators can migrate and enter blood vessels leading them to the bloodstream and can contribute to conditions such as cardiovascular disease and diabetes (18,20).

1.2.1. Stages of periodontal disease

Periodontal disease advances through a series of stages. It begins with redness, inflammation, pain, and bleeding of gums, especially when brushing or flossing, also known as gingivitis. This inflammation is due bacteria accumulating in biofilms around the gingival line and forming bacterial plaque. In gingivitis, the probing depth of the patient is physiological (3mm or less) and it is a reversible process, which means that with a professional cleaning done at the clinic using an ultrasonic tip and proper oral hygiene the gingivitis can be reversed and cause no

damage to the surrounding tissues of the teeth (18,20). However, if left untreated, gingivitis will progress into periodontitis, which is a chronic process and is considered irreversible.

In periodontitis the supporting structures of the teeth are affected on a deeper level and worsen over time. The inflammation goes below the gum line creating periodontal pockets where bacteria fester and can cause tissue or even alveolar bone loss over time (18). The probing depth of the patient is pathological (4mm or more) and with the constant affectation of the surrounding tissues and the alveolar bone, the pockets could get bigger resulting in loosened teeth and, ultimately, tooth loss. Periodontitis itself is divided into stages and grades according to the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions, which was published in 2018 which is an updated version of the 1999 classification (21). In the new classification, there is a table that divides periodontitis into four stages taking into account severity and complexity of tissue destruction, attachment and bone loss. As for the grading, the table classifies periodontitis into three grades taking into consideration primary criteria such as radiographic bone loss and also grade modifiers such as smoking and diabetes (21). In relation to diabetes, a grade A progression would be in a normoglycemic individual, or without a diabetes diagnosis, a grade B progression would be in an individual with HbA1c < 7% and a grade C progression would be in those having an HbA1c > 7%. With periodontitis being an irreversible condition, this indicates to us that it is of utmost importance to detect it at its earliest stages and treat it adequately before it proliferates (19).

1.2.2. Treatment of periodontal disease

Early detection and treatment of periodontal disease is crucial as it could have some severe consequences on oral health. There are different ways to treat periodontitis, and the approach could be non-surgical or surgical or a combination of both. These techniques allow to reduce the infection and inflammation and control the advancement of the disease while intending to restore periodontal health. The treatment starts with the non-surgical approach also called non-surgical periodontal therapy (NSPT), a comprehensive yet non-invasive treatment approach in which a scaling and root planning (SRP) is performed. It consists in an in-depth subgingival cleaning of the pockets. The goal of this procedure is to eliminate bacterial plaque and tartar from tooth and root surfaces using manual curettes, allowing to decrease the bacterial load and stopping the disease's progression (22). In order to control bacterial proliferation and better clinical outcomes, we usually supplement this treatment with oral antimicrobial rinses such as chlorhexidine rinses (23). Moreover, adjunctive therapies such as

anti-inflammatory agents, nutritional supplements, or medications can be added to NSPT to improve periodontal healing (23).

The other type of treatment is the surgical treatment, which is employed when the use of non-surgical methods is not enough for the case of the patient. In these procedures, a flap can be lifted that allows a direct access to the periodontal pocket and the root surface and a more in-depth cleaning of both. Other supplementary surgical techniques including guided tissue regeneration (GTR) or bone grafting permit the renewal of lost bone and soft tissue, reestablishing the tooth-supporting structures. The combination of these methods allows a good management of periodontitis as well as an opportunity for tissue regeneration (22,23).

1.2.3. What's its impact on oral and systemic health

Periodontal disease has a significant impact on oral health as it affects most of its tissues. Starting with the festering of pathological microorganisms which accumulate to form the bacterial plaque that inflame the gums, a condition also known as gingivitis, to the development of periodontitis if left untreated (18). The latter condition causes irreversible damage to soft tissues and destruction of alveolar bone creating periodontal pockets ultimately leading to tooth mobility and loss (24). Beyond these local effects, periodontal disease also has systemic implications, as bacteria and inflammatory mediators from infected periodontal tissues can enter the bloodstream, causing a low-grade chronic inflammatory response.

This widespread inflammation has been linked to a higher risk of several long-term conditions, such as heart disease, diabetes, and respiratory infections (25). The systemic effects of periodontal disease are particularly concerning for individuals with pre-existing conditions, as inflammation can exacerbate other health issues.

1.3. Link between T2DM and periodontal disease

The link between T2DM and periodontal disease is well known and studied, as each one of these conditions affect the other on an evolution and severity level. Diabetes diminishes immune responses that lead to a chronic systemic inflammatory state. This makes individuals with T2DM more vulnerable to infections, including periodontal disease as one of them (20).

Chronic hyperglycemia helps pathogenic bacteria to proliferate and promotes the generation of advanced glycation end products (AGEs), which is a byproduct of the combination between proteins and fats with sugars in the blood, through glycation. Is individuals with T2DM, this

phenomenon happens way more and leads to a disruption of the tissue repair system in the gingiva and structures supporting teeth (25,26).

Furthermore, with the elevation of levels of gum inflammation, tissue damage, and bone loss, this can exacerbate type 2 diabetes by promoting systemic inflammation(20). Indeed, the bacteria present in the pockets of periodontal patients can enter the bloodstream, Elevating levels of inflammatory agents, including pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α). The presence of these cytokines lead to more insulin resistance and worse glycemic control (20,26).

An integrated strategy is therefore necessary for the care of both illnesses since research indicates that periodontal therapy can lower HbA1c levels in diabetic patients by improving glycemic control (20,27). This link between both diabetes and periodontal disease shows us that it is of utmost importance to control dental health patients with T2DM to reduce overall complications and enhance general health.

1.3.1. Geographical and demographical prevalence

The worldwide geographical and demographical prevalence of T2DM and periodontal disease is very diverse and shows a wide variety between regions and populations. Many factors influence this range such as genetic predisposition, healthcare access and socioeconomic status. Globally, type 2 diabetes has become an epidemic, with the United States, China, and India accounting for most cases (28,29). Furthermore, different groups are affected by periodontal disease at different rates, showing that those with T2DM are more likely to develop it. For example, it is shown that more than 95% of patients with T2DM in India suffer some kind of periodontal damage, with the severity of the latter being related to a lack of dental hygiene and poor glycemic management (29,30). Therefore, the necessity for public health initiatives and integrated care plans that address both type 2 diabetes and periodontal disease is shown, especially in high-risk and underprivileged groups (28,30).

1.4. Justification

In today's world, as healthcare professionals, it is important to treat a patient with a holistic approach, encompassing all aspects and not solely focusing on a pathology. The relationship between T2DM and periodontal disease constitutes a critical intersection between oral and systemic health, where periodontal disease is no longer considered an isolated oral

condition but could also be a manifestation of broader systemic inflammatory processes, particularly in patients with chronic diseases like T2DM. Understanding their relationship is essential to treating both conditions.

In dentistry, recognizing the influence of systemic diseases on oral health is crucial for early diagnosis, prevention, and comprehensive patient care. Oral manifestations may often help the early diagnosis of diabetes, putting us dental professionals in an important position to assist patients with such conditions and promotes interdisciplinary collaboration with their healthcare providers to enhance patient outcomes and quality of life.

2. OBJECTIVE

To investigate the bidirectional relationship between T2DM and periodontal disease, focusing on epidemiology, pathophysiological link and clinical management.

3. MATERIAL AND METHODS

In order to conduct this literature review, an in-depth bibliographic search has been conducted using various sources, including the CRAI Dulce Cachón library that offers a wide range of books and articles as well as various reliable data bases such as PubMed, Google Scholar and Medline Complete. The main source used for this research was PubMed and the CRAI Dulce Cachón library, where the search terms and key terms included were the following: diabetes mellitus, Type 2 diabetes, periodontal disease, epidemiology, hyperglycemia, complications, HbA1c, fasting blood glucose, pathophysiology, periodontal health, periodontitis. The advanced research equations used in the databases were *"type 2 diabetes mellitus"* AND *"periodontal disease"*; *"type 2 diabetes mellitus"* AND *"pathophysiology"*; "*type 2 diabetes mellitus*" AND "*HbA1c*" AND "*fasting blood glucose*"; "*type 2 diabetes mellitus*" AND "*periodontal disease*" AND "*epidemiology*". Out of 322 articles, a few were chosen for this review with the application of filters such as "articles of the last 10 years" and "full free text".

The article selection was done according to inclusion and exclusion criteria that are presented in table 2.

The PICO research question that was formulated in order to find the objective of this study is as follows: in patients with type 2 diabetes mellitus (participants), is there a bidirectional relationship between T2DM and periodontal disease (intervention), compared to those without type 2 diabetes (comparison) in the overall periodontal health (outcomes), focusing on epidemiology, pathophysiological link and clinical management.

By defining this question leading us to our objective, a more accurate selection and analysis of relevant articles and body of literature can be achieved allowing us to get a more in depth understanding of the topic.

Inclusion criteria	**Exclusion criteria**
Scientific articles published between 2014 and 2024	Scientific articles published before 2014
Articles from reliable data bases (PubMed…)	Articles from unreliable sources
Articles written in English	Articles in other languages than English
Information relevant to type 2 diabetes mellitus and periodontal disease	Information not pertinent to the subject of the thesis such as other types of diabetes

Table 2. Inclusion and Exclusion criteria

4. RESULTS

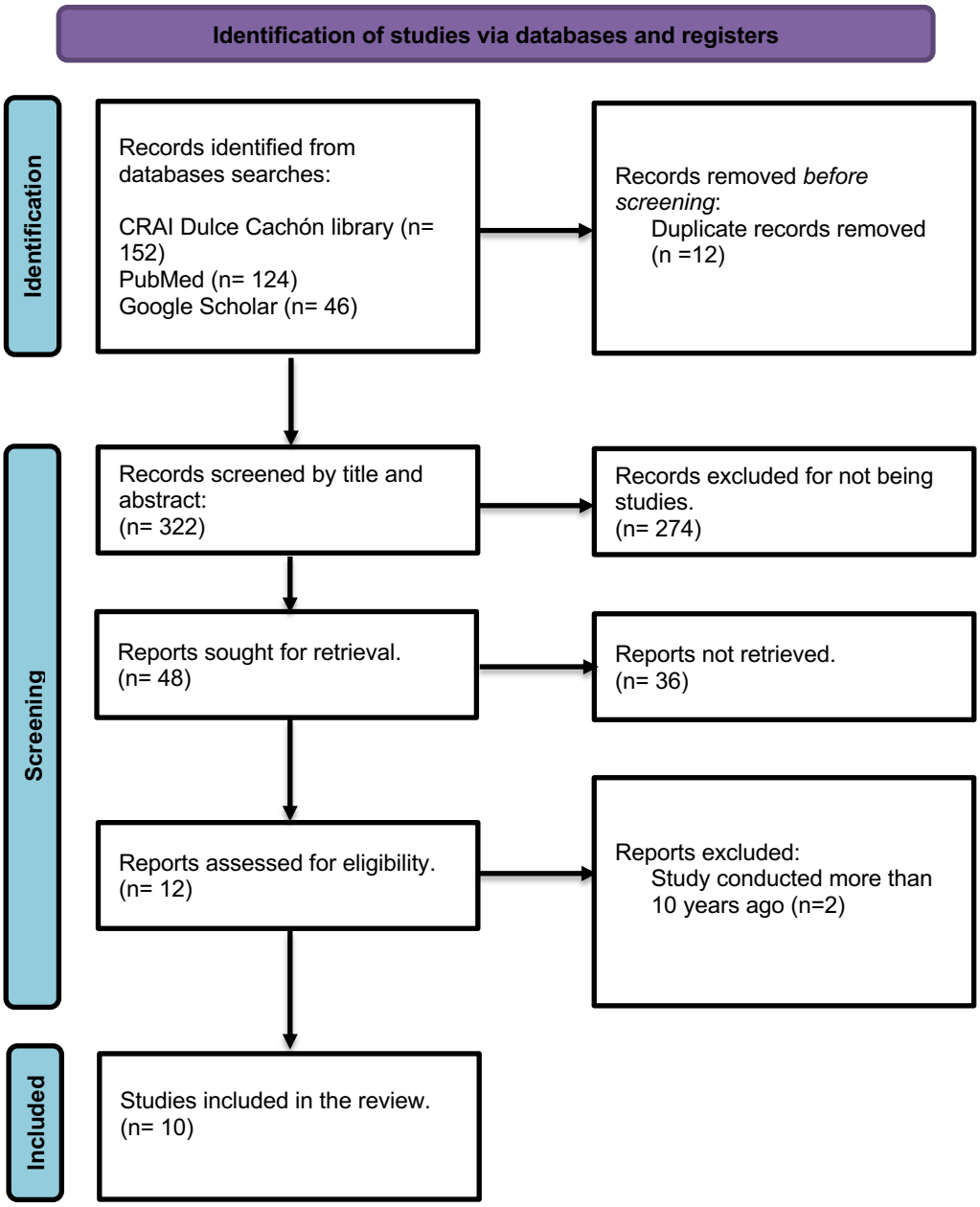

Figure 1. PRISMA Flowchart of the included reports in the study (31).

	Year and authors	Country	Type of study	Sample size (n)	Age range	Objective	Summary of the study	Outcomes
1	2023, Simna Pattayil et al. (32)	India	Cross-sectional study	260	30 to 60 years	Study that assessed the severity of periodontal disease by measuring periodontal inflamed surface area (PISA), clinical attachment loss (CAL), and HbA1c levels in patients with T2DM.	Compared 2 groups: Group 1: 130 individuals with T2DM treated with oral antidiabetic drugs (OAD) Group 2: 130 patients with T2DM treated with insulin therapy.	- Patients with higher HbA1c (>8.4%) had a significantly higher PISA (1347.89 mm^2). - Significantly lower periodontal severity in patients treated with insulin vs. oral antidiabetic drugs (PISA median value 1347.89 mm^2 in patients on OAD vs. 654.85 mm^2 in patients treated with insulin therapy).
2	2023, Sylvia M.C. Todescan et al. (33)	Canada	Cross-sectional study	121	8 to 17 years and 11 months	Study that investigates the relation between poor glycemic control and a higher occurrence of periodontal disease between children and adolescents with T2DM.4/23/25 2:10:00 PM	Children and adolescents with T2DM had to respond to an oral health questionnaire and were subjected a full mouth oral evaluation.	- Increased risk of periodontitis in individuals with T2DM. 45.5% of the sample present a form of periodontal disease (10 (8.3%) mild, 36 (29.8%) moderate, and nine (7.4%) severe. - Risk factors for periodontitis increased in patients with worse glycemic control (HbA1c>9 %).
3	2023, Rajashri Abhay Kolte et al. (34)	India	Intervention study	60	30 to 60 years	Study that analyzed the effects of non-surgical periodontal therapy (NSPT) on HbA1c, and on the levels of inflammatory markers TNF-α, IL-10 and hs-CRP, in patients with T2DM and stage III periodontal disease.	Compared 2 groups: Group 1: 30 patients in the intervention group (underwent NSPT) Group 2: 30 patients in the control group.	- Augmented periodontal health in patients treated with NSTP. Decrease of HbA1c of 0.8% and decrease in proportions of inflammatory markers TNF-α and hs-CRP. - Increase in levels of anti-inflammatory cytokine IL-10 (from 5.64 to 12.21 pg/ml) leading to reduced periodontal inflammation.
4	2020, Waleed Ahmed Ismail et al. (35)	Malaysia	Retrospective Cross-sectional study	166	18 to 70 years	Study that evaluated patient records diagnosed with chronic periodontitis to see the effect of T2DM on chronic periodontitis severity.	Compared 2 groups: Group 1: 47 patients with T2DM and periodontitis (test group) Group 2: 119 patients with periodontitis only (control group).	- Increased risk of 2,4 times for periodontal attachment loss in the patients with T2DM. - Higher mean age in test group, with the male sex being slightly predominant. - High correlation between hyperglycemia levels and periodontal severity.4/23/25 2:10:00 PM
5	2019, Monika Singh et al. (36)	North India	Cross-sectional study	427	30 to 65 years	Study that measured the prevalence of periodontal disease and its correlation with glycemic control, among patients with T2DM.4/23/25 2:10:00 PM	A partial mouth periodontal examination (PMPE) was used as well as Gingival index (GI), Oral hygiene index-simplified (OHI-S), Debris index-simplified (DI-S), Calculus Index-Simplified (CI-S), probing pocket depth (PPD), and clinical attachment loss (CAL).	- Very high percentage of diabetic patients (95,1%) have some sort of periodontal disease -Poor glycemic control is linked to severe periodontitis, as it's prevalence in patients with good, fair and poor oral hygiene was found to be 0.8%, 17% and 24.9%, respectively.

								- Various periodontal parameters including OHI-S, GI, CAL and PPD increase as glycemic control (HbA1c %) decreases.
6	2020 Tatsuo Yamamoto et al. (37)	Japan	Cross-sectional study	2436	29 to 93 years	Study that evaluates the link between periodontal health and socioeconomic status in patients with T2DM.4/23/25 2:10:00 PM	Periodontal examination was conducted, and a chart was filled including Probing pocket depth (PPD), bleeding on probing (BOP), tooth mobility and number of teeth present, comparing outcomes based on education level.	- Worse periodontal health in patients with lower education (1.42 increased change of BOP and 1.58 increased chance of tooth mobility) versus university educated patients. - More teeth present in the mouths of university educated patients (42.1% had more than 27 teeth in the mouth vs. 18.5% in patients that have a junior high school diploma). 4/23/25 2:10:00 PM
7	2017 Winning L et al. (38)	United Kingdom	Prospective Cohort Study	1331	58 to 72 years	Study that aimed to analyze if periodontitis increases the risks of developing T2DM.	Followed a cohort of dentate non-diabetic men who received a periodontal evaluation and were monitored biannually through questionnaires over a median follow-up period of 7.8 years.	- Increase in the risk of developing T2DM by 1.69 times in patients with moderate to severe periodontitis in contrast with those with no/ mild periodontitis. - Furthermore, men with moderate to severe periodontitis presented less education years and were often from a lower socio-economic background.
8	2024 Fatemeh Tavakoli et al. (39)	Iran	Cross-sectional Study	90	40 to 60 years	Study that compared levels of salivary matrix metalloproteinase-8 (MMP-8), a biomarker linked to inflammation and tissue degradation in diabetic and diabetes-free patients with periodontitis.	Patients had a saliva sample analysis after 12 hours without brushing their teeth (39). Group 1: 30 patients with periodontitis and T2DM Group 2: 30 patients with periodontitis without T2DM Group 3: 30 patients in the control group. 4/23/25 2:10:00 PM	- Higher levels of MMP-8 found in the group where patients had periodontitis and T2DM. Fasting blood glucose and levels of salivary MMP-8 protein have a significant positive correlation in this group, with a mean of 450 ng/ml compared to 380 ng/ml in the group of patients with periodontitis without T2DM and 200 ng/ml in the control group.
9	2024 Alarcón-Moreno et al. (40)	Mexico	Quasi-experimental study	45	18 to 60 years	A study that evaluated the effect of periodontal therapy with zinc and magnesium on oxidative stress and periodontal health in individuals with T2DM.	Compared 2 groups: Group 1: 19 patients subjected to non-surgical periodontal therapy (NSPT) only (control group) Group 2: 20 patients subjected to NSPT with an oral supplement of	- Overall reduction in periodontal parameters (periodontal probing depth PPD, bleeding on probing BoP, periodontal inflamed surface area PISA and dental bacterial plaque index DBPI) in both groups after periodontal intervention.

							500 mg of magnesium oxide and 50 mg of zinc gluconate for 30 days following treatment (experimental group).	- Greater decrease in the experimental group versus the control group with some parameters such as PPD (decreased by 0.77 mm in the control group and by 1mm in the experimental group).
10	2024 Marwa Y. Shaheen et al. (41)	Saudi Arabia	Cross-sectional study	160	≥ 18 years	Study that evaluated the correlation between whole salivary prostaglandin E2 (PgE2) and HbA1c taking into account periodontal parameters including plaque index, gingival index, probing depth, and clinical attachment loss. 4/23/25 2:10:00 PM	Unstimulated whole saliva samples were collected from participants in 4 groups and the PgE2 levels were compared: Group 1: diabetics with periodontal inflammation (PI), Group 2: diabetics without PI, Group 3: non-diabetics with PI Group 4: non-diabetics without PI).	- Diabetics with PI had significantly higher PgE2 levels (202.6 ± 66.71 pg/mL) in contrast to other groups: diabetics without PI (31.5 ± 9.77 pg/mL), non-diabetics with PI (96.9 ± 39.5 pg/mL), and non-diabetics without PI (24.02 ± 10.6 pg/mL). -The first group also showed higher overall values in periodontal parameters, such as probing depth, which was on average 4.85 mm in the 1st group, 2.95 mm in the 2nd, 3.92mm in the 3rd and 2.68mm in the 4th.

Table 3. Table summarizing the 10 studies demonstrating a relationship between T2DM and periodontal disease.

5. DISCUSION

5.1. Epidemiological link between T2DM and periodontal disease

5.1.1. Prevalence and risk factors for periodontitis

Comparing the findings encountered in the results table above, we can assert that there is a strong association in epidemiological regards when talking about T2DM and periodontal disease. Singh et al. (2019) showed that individuals with T2DM present a high prevalence of periodontal disease with a staggering 95.1% of diabetic patients exhibiting some sort of periodontal disease (36). Furthermore, assessing some periodontal parameters, Ismail et al. (2020) found that there is an increased risk of 2,4 times for periodontal attachment loss in the patients with T2DM (35).

Other authors, Pattayil et al. (2023) when assessing periodontal inflamed surface area (PISA), demonstrated that patients presenting higher HbA1c (>8.4%) had a significantly higher PISA (1347.89 mm^2) (32).

Diabetes is a notable risk factor contributing to the emergence of periodontitis, and it's severity is correlated with poorly controlled hyperglycemia (26). This finding is supported by the results in the studies 4 and 5, in which Ismail et al. (2020) demonstrated a high correlation between hyperglycemia levels and periodontal severity (35) and Singh et al. (2019)'s results proved that poor glycemic control is linked to severe periodontitis, as it's prevalence among patients with varying levels of oral hygiene; good, fair, and poor, was found to be 0.8%, 17% and 24.9%, respectively (36). Also periodontal indicators including Gingival index (GI), Oral hygiene index-simplified (OHI-S), probing pocket depth (PPD), and clinical attachment loss (CAL) increase as glycemic control (HbA1c %) decreases (36), which backs the claim that poorer glycemic control is correlated with worsening periodontal condition. Todescan et al. (2023) showed that severity of periodontitis is linked to HbA1c levels, as risk factors for periodontitis increased in patients with worse glycemic control (HbA1c>9 %) (33).

5.1.2. The role of periodontitis in increasing the risk of diabetes

Wu et al. (2020)'s systematic review reports that patients with periodontitis were found to have a greater prevalence of T2DM (odds ratio [OR]=4.04) and those with T2DM showed worse overall periodontal health, with deeper periodontal pockets (by an average of 0.61 mm), increased attachment loss (0.89 mm), and greater tooth loss (approximately two more teeth

lost compared to non-diabetics) (25). This goes to show the bidirectional association between both conditions, how glycemic control affects periodontal disease and its severity, on the other hand how periodontal disease also has a link with glycemic control. Winning L et al. (2017) showed how there's an increase in the risk of developing T2DM by 1.69 times over a 7.8 year follow-up period in individuals with moderate to severe periodontitis in contrast with those with who had no/ mild periodontitis (38), which supports the claim the periodontitis also affects hyperglycemia.

5.2. Pathophysiological relation between type 2 diabetes and periodontal disease

5.2.1. Underlying biological mechanisms: Inflammatory Pathways and Immune Dysregulation

There is an intertwined relationship between T2DM and periodontal disease that has an underlying biological mechanism and that is mediated primarily by chronic inflammation and dysregulated immune responses. The activity of insulin is a primordial process in regulating blood glucose levels and sustaining the body's homeostatic balance, therefore the mechanisms that are linked to insulin's release and detection are tightly controlled and any disturbance in them causes a metabolic imbalance at various levels, leading to chronic inflammation (13) or persistent pro-inflammatory state. This state is distinguished by high levels of pro inflammatory cytokines (tumor necrosis factor-alpha (TNF-α) and Interleukin-6 (IL-6)) and markers (C-reactive protein (CRP)) which promotes insulin resistance (34).

Kolte et al. (2023) demonstrated that patients presenting T2DM and periodontitis had increased levels of inflammatory cytokines. In addition, the levels of those inflammatory markers decrease as there is an increase in periodontal health through non-surgical periodontal therapy (NSPT). Furthermore, an increase in levels of anti-inflammatory cytokine IL-10 (from 5.64 to 12.21 pg/ml) led to reduced periodontal inflammation and increased glycemic control (33), which supports the claim that periodontal inflammation contributes to systemic metabolic control impairments, and chronic hyperglycemia has a role in altering the immune response. This finding is supported by other research that states that a persistent low-grade inflammation in diabetic patients, also called "metaflammation" induces chronic immune activation and an increase in inflammatory markers which in-turn leads to glycemic instability and an increase in periodontal breakdown (13).

Other research also aligns with this finding and underlines a clear biological mechanism linking T2DM and periodontal disease. Tavakoli et al. (2024) showed a biochemical link by measuring salivary matrix metalloproteinase-8 (MMP-8), a biomarker associated to inflammation and

periodontal tissue degradation. It was revealed that diabetic patients with periodontitis had higher levels of MMP-8, also supporting that hyperglycemia increases inflammatory susceptibility (39).

5.2.2. Oxidative Stress and Impaired Healing Mechanisms

Another biological aspect affected in the bidirectional relationship between T2DM and periodontal disease is oxidative stress which is a key player in the dysregulation of healing mechanisms in diabetics (42). Constant high blood glucose results in the formation of advanced glycation end-products (AGEs). The AGEs, when binding to the corresponding receptors (RAGE), trigger the development of reactive oxygen species (ROS), inducing inflammation, weakened tissue repair and insulin resistance (26,42). Furthermore, dysfunctional fibroblasts, reduced collagen synthesis, and impaired angiogenesis which lead to vascular damage, cause further periodontal breakdown and delayed healing in those patients (42).

Shaheen et al. (2024)'s research showed that a key marker of inflammation, whole salivary prostaglandin E2 (PgE2), is present in higher levels in diabetics with periodontitis (202.6 ± 66.71 pg/mL), in comparison with non-diabetics with periodontitis (96.9 ± 39.5 pg/mL) and healthy controls (24.02 ± 10.6 pg/mL)(41). This study suggests that hyperglycemia heavily influences inflammatory pathways and impairs healing mechanisms, leading to periodontal destruction.

This "metaflammation" state in diabetics therefore exacerbate these processes, which leads to an increase in bleeding on probing, probing depth, and periodontal attachment loss in diabetic patients compared to non-diabetics.

5.3. Clinical management in individuals with T2DM and periodontal disease

5.3.1. Periodontal Therapy and Glycemic Control Improvement

Understanding and navigating diabetes and periodontal disease is crucial through an effective clinical management. The objective of these clinical strategies is to increase overall periodontal health, improve metabolic control and ultimately prevent the progression of both diseases. Non-surgical periodontal therapy (NSPT), widely considered as the first-line treatment for periodontal disease, refers to a non-invasive approach comprising scaling and root planning and adjunctive antimicrobial therapy, and host modulation therapy without requiring surgical intervention (34).

Through the study, Kolte et al. (2023) showed that NSPT decreased levels of inflammatory markers TNF-α and hs-CRP, as well as levels of glycated hemoglobin HbA1c by 0.8%, while it increased in levels of anti-inflammatory cytokine IL-10 (from 5.64 to 12.21 pg/ml) leading to reduced periodontal inflammation and improved glycemic control (34).

In another study, Tavakoli et al. (2024) underlines that NSPT can significantly decrease proportions of salivary matrix metalloproteinase-8 (MMP-8), an inflammatory enzyme strongly linked to tissue destruction in periodontitis (39). This proves that treating periodontitis can improve the overall systemic metabolic state of a person by managing periodontitis but also acting on biochemical inflammatory markers.

Furthermore Kocher et al. (2018) demonstrated that there could be a direct systemic benefit following NSPT as the review of studies showed that periodontal therapy may reduce HbA1c levels by around 0.4% to 0.6% over six months (26).

5.3.2. Host Modulation and other therapies

Some therapies, beyond traditional mechanical periodontal treatment, have emerged giving an array of options in the clinical management of periodontal disease. By combining these new therapies, to traditional NSPT in diabetic patients, we are able to modulate inflammatory pathways, making it easier to tackle both diseases (40). These therapies include nutritional supplementation, Host modulation therapies and pharmacological agents.

Regarding nutritional supplementation, Alarcón-Moreno et al. (2024), who evaluated the effect of periodontal therapy with zinc and magnesium in patients with T2DM showed that supplementing traditional periodontal therapy with zinc and magnesium led to greater reductions in oxidative stress markers and improved periodontal health compared to patients treated with NSPT alone (40). These studies suggest the fact that nutritional supplementation can increase the efficacy of periodontal treatment. We could also imply that supplementing diet with essential minerals such as zinc and magnesium could potentially have a supportive role in accompanying periodontal treatment in diabetic individuals.

Another therapy that could help accompany traditional treatment would be using biomarkers for monitoring inflammation. In fact, Shaheen et al. (2024)'s study showed that diabetic with periodontal disease had the highest levels of whole salivary prostaglandin E2 (PgE2) compared to other groups, which could suggest this inflammatory biomarker could be

used to measure and monitor response to periodontal treatment and progression of the disease in diabetic patients (41).

Host modulation therapy is another alternative therapy that consists in targeting excessive inflammation and oxidative stress instead of only focusing on the pathogenic bacteria causing periodontitis. This emerging approach uses anti-inflammatory agents, antioxidants, and enzyme inhibitors to accelerate the healing process in diabetics with periodontal disease and impede periodontal tissue destruction (43). Studies show that treating systemic inflammation with host-modulatory agents such as statins, omega-3 fatty acids, and disease-modifying anti-rheumatic drugs (DMARDs) can improve periodontal outcomes (23). In fact, omega-3 fatty acids and aspirin had an effect on inflammatory cytokines, by lowering their levels in periodontal tissues, also studies show that statins reduced periodontal inflammation and improved bone preservation (23).

As for pharmacological therapy, the use of adjunctive pharmacological agents has shown to reduce periodontal inflammation in diabetic patients (23,43). These agents can target specific inflammatory biomarkers such as IL-6 and TNF-α and help reduce inflammatory cytokine expression. For instance, Tocilizumab, which binds to IL-6 receptors and acts as an inhibitor, allows to decrease the levels of this biomarker, therefore decreasing periodontal inflammation (23). This is underlined in the findings by Pattayil et al. (2023), which suggests that there is a direct relation between inflammatory markers (TNF-α, hs-CRP) and periodontal disease severity in patients with T2DM. Furthermore, the findings from this study proved that there was a variation in the outcomes between patients treated with insulin versus oral antidiabetic drugs (OAD). The insulin-treated group presented lower periodontal inflammation compared to those on OADs, with a significantly reduced periodontal inflamed surface area (PISA)(32). This supports the finding that pharmacological intervention can influence periodontal therapy.
These studies underline the importance of a proper clinical management with a combined approach, using conventional NSPT as well as alternative therapies to address periodontal disease in diabetic patients.

5.4. Limitations to the results

After discussing epidemiology, pathophysiology and clinical management relating T2DM and periodontal disease, the findings strongly support a bidirectional relationship between both conditions, however it is important to consider the various limitations to the results presented.

5.4.1. Limitations regarding type of study

First, we should look at the type of studies chosen for the results table, as 7 out of 10 of these studies are cross-sectional, this poses a limitation in establishing a direct causal link between hyperglycemia and periodontal status as they only represent data from a single point in time and do not study patients longitudinally. While these findings can establish an association between diabetes and periodontal disease, they can't determine whether poor glycemic control causes periodontal disease or the opposite.

Furthermore, another variable to be taken into account are the variations in study designs, sample sizes, and diagnostic criteria for both T2DM and periodontitis in the various studies presented. In fact, the differences between these variables lead to heterogeneity in the outcomes, which make direct comparisons difficult.

5.4.2. Limitations in cofounding variables

To grasp the effect of diabetes and periodontitis on overall health, it is of utmost importance to take into account the contribution of confounding factors, such as lifestyle habits, smoking, medication, genetic predisposition, socio-economic class, and access to healthcare, that could also impact results, potentially overestimating or underestimating the association between the two diseases.

Yamamoto et al. (2020) evaluated the link between periodontal health and socioeconomic status in patients with T2DM and found that patients with lower education had worse overall periodontal health (1.42 increased change of BOP and 1.58 increased chance of tooth mobility) in comparison with university educated patients. These findings show that low education is associated with worse periodontal health, increased tooth mobility, and a higher likelihood of bleeding on probing and further underlines the fact the cofounding variables could play a big role in the impact of both conditions on each other.

5.4.3. Limitations of biomarker studies

Lastly, while biomarker studies including levels of IL-6, TNF-α, and MMP-8, provide a view into inflammatory mechanisms, they do not fully capture the complex interplay between host response,

microbiome composition, and metabolic dysfunction in diabetic patients with periodontitis. The variations noticed in biomarker levels could also be influenced by external factors such as habits, diet, medication, and genetic predisposition making it difficult to rely on these markers as tools for diagnostic criteria.

5.5. Future directions

The integration of periodontal therapy into diabetes care protocols is a promising strategy for improving both metabolic and oral health outcomes. Given that even a slight reduction in HbA1c significantly lowers diabetes-related complications, periodontal treatment should be considered a standard preventive measure for diabetic patients (44). However, the long-term benefits of adjunctive pharmacological therapies in periodontal management remain an emerging area of research, requiring well-designed clinical trials to confirm their effects on the long term.

To strengthen the evidence supporting integrated treatment approaches, future studies should focus more on standardized methodologies and longitudinal data, tracking the same individuals over time and allowing us to establish causality.
Additionally, exploring personalized treatment strategies, including anti-inflammatory therapies, host modulation therapy, and customized periodontal interventions, could optimize outcomes for diabetic patients.

Finally, oral manifestations can be an important indicator for suspecting undiagnosed diabetes, as symptoms such as persistent gingival inflammation, delayed wound healing, xerostomia, and increased susceptibility to infections may signal underlying metabolic dysfunction, so it is primordial for us as dentists to know the oral manifestations related to periodontal disease and diabetes and inform the patient to interconsult with his healthcare provider in case of doubts.

6. CONCLUSIONS

1. This thesis aimed to investigate the bidirectional relationship between type 2 diabetes mellitus (T2DM) and periodontal disease, with a focus on three core dimensions: epidemiological patterns, pathophysiological mechanisms, and clinical management strategies. Through the analysis of current literature and key clinical studies, it has become clear that this relationship is both significant and multifactorial, requiring an interdisciplinary approach to both research and patient care.

2. From an epidemiological point of view, the evidence demonstrates that individuals with T2DM have a notably higher prevalence and severity of periodontal disease, particularly those with poor glycemic control. On the other hand, periodontitis has been shown to increase the risk of developing T2DM, especially in cases of chronic inflammation. This highlights a critical public health issue: periodontal status may serve not only as a marker of glycemic instability but also as a potential early indicator for undiagnosed diabetes. These findings show the need of integrating routine oral health assessments into diabetic screening and management protocols.

3. In terms of pathophysiological mechanisms, the two conditions are linked by common inflammatory and metabolic pathways particularly involving cytokines like TNF-α, IL-6, and oxidative stress mediators. Chronic hyperglycemia in T2DM leads to an upregulation of these pro-inflammatory cytokines, alongside increased oxidative stress and the formation of advanced glycation end-products (AGEs). These mechanisms contribute to periodontal tissue destruction, delayed wound healing, and immune dysfunction. Meanwhile, periodontitis itself can exacerbate insulin resistance and systemic inflammation. The elevated levels of biomarkers such as MMP-8 and prostaglandin E2 (PgE2) in diabetic patients with periodontitis further support the biological connection.

4. When it comes to clinical management, the research confirms that non-surgical periodontal therapy (NSPT) significantly reduces periodontal inflammation and is associated with improvements in glycemic control. A decline in HbA1c levels of even 0.3% which is achievable through periodontal treatment, can lead to decreased risk of diabetes-related complications. Adjunctive strategies, including host modulation therapies, nutritional supplementation and pharmacological agents have also shown to enhance treatment outcomes, particularly in patients with poorly controlled diabetes.

7. SUSTAINABILITY

A sustainable approach to managing T2DM and periodontal disease requires addressing social, economic, and environmental factors to improve long-term health outcomes. Socially, increasing awareness regarding the complex relationship between diabetes and periodontal disease is primordial for early diagnosis and prevention. Integrating oral health screenings into primary diabetes care can enhance accessibility, particularly for disadvantaged populations who face challenges with both dental and medical care. Educational campaigns promoting oral hygiene, healthy diets, and lifestyle modifications can further reduce disease progression.

From an economic perspective, effective periodontal disease management in diabetic patients can significantly lower healthcare costs by reducing complications associated with poor glycemic control, such as cardiovascular disease and kidney failure. Investing in preventive care and non-surgical periodontal therapy (NSPT) can decrease the need for expensive treatments, benefiting both healthcare systems and patients.

Environmentally, sustainable dentistry practices, such as reducing the use of single-use plastics, implementing digital records, and promoting biodegradable dental materials can minimize waste. Additionally, encouraging diets which are rich in anti-inflammatory nutrients supports both systemic health and environmental sustainability. A holistic, sustainable healthcare approach that integrates oral and systemic disease management can improve patient well-being while reducing long-term economic and environmental costs.

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