GRADUATION PROJECT

Degree in Dentistry

DIABETES AND ORAL HEALTH.
MANAGEMENT OF DIABETIC PATIENTS.

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ABSTRACT

Introduction: Diabetes is a chronic metabolic condition that alters the body's ability to regulate glucose levels resulting from a deficiency in insulin or insensitivity related to this hormone. Diabetes affects millions of people in the world and has been linked to various oral complications. Therefore, managing the oral health of patient with diabetes is crucial to improve their overall health outcomes. **Objectives:** The principal objective of this study is to describe the principal oral manifestations linked with diabetic patients. Two specific objectives were conducted in addition: to put in evidence the bidirectionality between periodontitis and diabetes, and to describe a new non-invasive method to diagnose diabetic through salivary biomarker. **Methods:** To describe the relationship of diabetes and oral health, this paper conducted a comprehensive review of 11 relevant studies sourced from Medline to answer our objectives. **Results:** The review highlights a significant association between diabetes as a risk factor of periodontitis, oral candidiasis, xerostomia and mucosal lesions. A bidirectionality has been observed between periodontitis and diabetes, patients with periodontitis have higher chance to develop diabetes. Study also demonstrated the importance to perform an early diagnosis with new methods explored such as salivary biomarker. **Conclusions:** The interrelation between diabetes and oral health requires a holistic approach in the management of diabetic patients, as every oral health manifestation can exacerbate one another. Health professionals must be aware of the bidirectional relationship between diabetes and periodontitis and the importance of individualized treatment planning. Early diagnosis and proper management of oral complications in diabetic patients are critical to prevent their progression and improve their quality of life.

Key words: *Dentistry; oral health; diabetes mellitus; periodontitis; management.*

RESUMEN

Introducción: La diabetes es una afección crónica que altera la capacidad del cuerpo para regular la glucemia debido a una deficiencia en la insulina o insensibilidad a esta hormona. La diabetes afecta a millones de personas en todo el mundo y se ha relacionado con varias complicaciones orales. Es crucial manejar la salud oral del paciente diabético para mejorar su salud en general. **Objetivos:** El objetivo principal de este estudio es describir las principales manifestaciones orales en pacientes diabéticos. Se establecieron dos objetivos específicos: evidenciar la relación bidireccional entre periodontitis y diabetes, y detallar un nuevo método no invasivo para el diagnóstico de diabetes mediante biomarcadores salivales. **Métodos:** Este estudio revisó 11 estudios exhaustivamente para describir la relación entre diabetes y salud oral. Las búsquedas se realizaron en la base de datos Medline. **Resultados:** La revisión destaca una asociación significativa entre la diabetes como factor de riesgo de periodontitis, candidiasis oral, xerostomía y lesiones mucosas. Se observó una

bidireccionalidad entre la periodontitis y la diabetes, los pacientes con periodontitis tienen una mayor probabilidad de desarrollar diabetes. Además, el estudio demostró la importancia de realizar un diagnóstico temprano con nuevos métodos explorados como el biomarcador salival. **Conclusiones:** La interrelación entre la diabetes y la salud oral requiere un enfoque holístico en el manejo de pacientes diabéticos, ya que cada manifestación de salud oral puede exacerbar la otra. Los profesionales de la salud deben ser conscientes de la relación bidireccional entre la diabetes y la periodontitis y la importancia de la planificación del tratamiento individualizada. El diagnóstico precoz y el manejo adecuado de las complicaciones orales en pacientes diabéticos son fundamentales para prevenir su progresión y mejorar su calidad de vida.

Palabras clave: *Odontología; salud bucal; diabetes mellitus; periodontitis; gestión.*

1. TABLE CONTENT

2. INTRODUCTION

2.1. Diabetes

Diabetes mellitus (DM) is a chronic medical condition caused by a dysfunction of the metabolic system. The pathology is mainly caused by a deficiency in insulin or insensitivity to this hormone, increasing glycemia (1).

2.1.1 Diabetes classification

There are 3 types of diabetes:

- Type 1 diabetes (T1D) also called “insulin-dependent”, due to a lack of insulin secretion by the pancreas. Onset of this type of diabetes affects young people mainly due to genetic factors and are not usually in appearance overweight (2). But also, due to some environmental factors like virus infection in young people (cytomegalovirus, coxsackievirus, mumps, rotavirus and enteroviruses). Those viruses harm β cells of the islets of Langerhans in the pancreas and trigger autoimmunity (3).
- Type 2 diabetes (T2D) also called “non-insulin-dependent”, due to a reduction of insulin sensitivity by the body's cells or insufficiency of insulin production. T2D is caused mainly by environmental factors such as eating habits, lack of sports, high sugar consumption, air pollution... (4). But also, the aetiology might be genetics (5)**.**
- A third type of diabetes is called “gestational diabetes” (GD) affecting pregnant women. Characterised by a glucose intolerance due to hormones (placental) which generally disappear after childbirth (6). GD affects around 20% of pregnant women and evolves into T2D in around 50% of them in the next 10 years (7).

Classification is essential for determining appropriate treatment, some people may not fit clearly into either T1D or T2D upon initial diagnosis. Traditional beliefs T2D only affects adults and T1D only affects children are no longer entirely correct, as both types of diabetes can affect people of any age (8). The classical method for suspecting DM is identifying the trio of symptoms consisting of excessive urination (polyuria), increased hunger (polyphagia), and excessive

thirst (polydipsia). T1D may develop in adults, and the onset of the disease may differ from that in children (9).

2.1.2 Insulin

The role of insulin is vital for the body: insulin is a peptide hormone secreted by the β cells of the islets of Langerhans located in the pancreas (10). It has an important role in the metabolism of carbohydrates, lipids and proteins by promoting the absorption of carbohydrates present in the blood by different cells, such as fat cells, liver cells or skeletal muscle cells. Glucose absorbed by these tissues is converted into glycogen or triglycerides. The main role of insulin is lowering the level of glucose in the blood (hypoglycaemic effect), therefore the release of glucose from liver into the blood is limited by high insulin concentration in the blood. Along with its antagonist hormone glucagon, they play both a major role in the regulation of glycemia. (1)

2.1.3. Standard values of diabetes

Symptoms of prediabetes are not clearly defined. To make an accurate diagnosis, it is necessary to understand the concept of values associated with diabetes. Impaired fasting glucose (IFG) and impaired glucose intolerance (IGT) are intermediate stages of abnormal glucose regulation that occur between normal glucose homeostasis and diabetes also called prediabetic state.

IFG is a prediabetic condition in which fasting glucose levels are higher than normal but less than the diagnostic threshold for diabetes mellitus. The World Health Organization (WHO) defines normal fasting blood glucose as less than 100 mg/dL (5.6 mmol/L), and IFG as a fasting blood glucose level between 100 mg/dL (5.6 mmol/L) and 125 mg/dL (6.9 mmol/L) as indicated in the Table 1. (11,12). IFG is a risk factor for developing T2D and may also be linked to other metabolic complications such as obesity, high blood pressure, dyslipidaemia (abnormal level of lipids in the blood), and cardiovascular disease. Fasting means no intake of calorie during the last 8 hours. (8)

Table 1. Values in fasting plasma glucose (FPG) (8).	
Result	**FPG values (mg/dL)**
Normal fasting glucose	< 100 mg / dL
Prediabetes or IFG (Impaired fasting glucose)	From 100 to 125 mg / dL
Initial diagnosis of diabetes	> 126 mg /dL

Impaired Glucose Tolerance (IGT), according to the American Diabetes Association (ADA), is a condition in which blood glucose levels are higher than normal but not high enough to be classified as diabetes. IGT is regarded as a stage in between normal glucose tolerance and diabetes. Individuals with IGT are more likely to develop T2D and cardiovascular disease. As indicated in the Table 2 the diagnostic criteria for IGT is a blood glucose level of 140 to 199 mg/dL (7.8 to 11.0 mmol/L) 2 hours after ingestion of a 75g oral glucose load during an oral glucose tolerance test OGTT (11,12). A person is considered to have normal glucose tolerance if his blood glucose level is less than 140 mg/dL (7.8 mmol/L) 2 hours after a glucose challenge. A person is diagnosed with diabetes if her blood glucose level is greater than or equal to 200 mg/dL (11.1 mmol/L) 2 hours after a blood glucose test. (8)

Table 2. Values in oral glucose tolerance test (OGTT) (8).	
Result	**OGTT (mg/dL)**
Normal glucose tolerance	< 140 mg / dL
Prediabetes or IGT (Impaired glucose intolerance)	From 140 to 199 mg / dL
Initial diagnosis of diabetes	> 200 mg /dL

A third alternative approach to diagnose prediabetes, instead of relying on glucose measurement, is to evaluate the glycated or glycosylated haemoglobin (HbA1c) level in the blood. HbA1c level is a blood test that measures the average amount of glucose over the past two to three months. The higher the blood sugar level, the more glucose that binds to haemoglobin, and the higher the HbA1c value. (9)

According to ADA and as indicated in the Table 3, the recommended HbA1c values for non-diabetics are less than 5.7%, for prediabetics are between 5.7% and 6.4% and diabetics are more than 6.5%. (8)

Table 3. Levels of HbA1c in the blood (8).

Result	HbA1c (in %)
Non-diabetic	< 5.7%
Prediabetes	5.7% to 6.4%
Diabetes	> 6.5%

It is important to note that these values are general guidelines and may vary depending on the individual's health status, age, diseases and other factors (8).

Unless symptoms are clear such hyperglycaemic crisis with typical symptoms and a random glucose test have been performed with more than 200mg/dL (11.1mmol/L), it is necessary to perform a second test to confirm diagnosis. If both first and second test are positive (OGTT > 200 mg/dL or FPG > 126 mg/dL or HbA1c > 6.5%) we will confirm a positive DM diagnosis.

2.2. Oral diseases linked with Diabetes Mellitus

2.2.1. Periodontitis

Periodontitis is a chronic inflammatory disease that progressively destroys the supporting tissues of the teeth leading to attachment and bone loss (AL and BL). Periodontitis usually develops following gingivitis that has not been properly treated with an accumulation of plaque and subgingival calculus (13). In periodontitis, deep periodontal pockets are formed in the periodontal tissue, then a proliferation of anaerobic microorganisms which are more virulent than those usually present in the case of simple gingivitis (14). This propagation of bacteria induces a destruction of periodontal tissues and alveolar bone and therefore causing tooth loss. (15)

There is current evidence based on several reviews on Medline search, as well as the relevant reference lists used by these reviews, that DM and periodontal diseases have a strong link. DM has a multifactorial adverse effect on biological

mechanisms affecting periodontal health. It appears there is more prevalence of periodontal diseases in children and adolescents with DM than in healthy ones. (16–20). In some study, gingivitis affect 97.6% of the diabetic patients (17).

The treatment of periodontitis requires professional subgingival dental curettage and a very scrupulous personal dental hygiene program. The most advanced cases may require antibiotic therapy associated with surgical treatment (14).

2.2.2. Oral fungal infections

Fungi are eukaryotic organisms that can lie to the external plasma membrane in the oral cavity. There are many types of Candida species for example: *C. albicans, C. glabrata, C. guillermondii, C. krusei, C. parapsilosis, C. pseudotropicalis, C. stellatoidea, C. tropicalis*. Of the 200 known species of Candida, about 20 are responsible for human infections. The most common fungal component present in the oral cavity is the *Candida albicans*. *C. albicans* is carried in the mouths of almost 50% of the population as a normal component of the oral flora. Although the mere presence of Candida in the oral flora is not considered a disease, oral candidiasis can occur when Candida species become pathogenic and invade host tissues. It can occur in the oral cavity due to local or systemic factors that alter immunity. To reach its symptomatic virulence potential, from its yeast form, *C. albicans* grows long enough filamentous called “hyphal growth” which allows to penetrate the underlying substrate. (21,22)

DM is a metabolic disorder that makes diabetics more susceptible to oral fungal infections, with higher prevalence when long-standing and poor controlled glycemia. The type *Candida albicans* has the highest prevalence in diabetic and non-diabetic patients. (23–25)

Different factors cause this higher prevalence of infection, firstly it may be due to a weakening of the immune system. Poor glycaemic control can alter vascularity, making smaller branches of the nervous and vascular system less accessible (this mechanism will be explained in more details in the section “*2.3.2.1. Hyperglycaemic impacts on oral health”*), impairing the immune system's ability to effectively reach and fight infection. (26)

Another factor would be a dysbiosis of oral microbiota in patient in cases of poor DM control. There is a balance in the microbiota in healthy patients, preventing apparition of infections like oral fungus. An unbalanced oral microbiota contributes in the apparition of new oral diseases (27). On the other side, patients with good control of their T1D do not present oral pathology but higher presence of bacteria as *Streptococcus* spp., *Actinomyces* spp. and *Rothia* spp. than healthy patients. *Candida albicans* is a risk factor for periodontal disease. (26) Oral fungus is directly acting jointly with pathogenic bacteria on periodontal disease, by inducing production of pro-inflammatory cytokines aggravating tooth attachment loss (28).

2.2.3. Xerostomia

Xerostomia is a condition of “dry mouth” associated with a lack of saliva, hyposalivation and a change in the saliva composition or consistency. Studies showed higher prevalence of xerostomia and salivary gland dysfunction in diabetic patients than non-diabetic patient (25,29,30). The symptoms are the following: “Extreme thirst, halitosis, alterations in food taste, dysphagia, unbalanced oral microbiota, dental and periodontal diseases and rampant teeth caries” (29).

Xerostomia is directly linked with oral diseases: by influencing salivary pH, the quality and consistency of saliva can have a direct impact on the oral microbiota. Poor saliva quality and consistency can result in dysbiosis, which can promote the development of oral fungal infections, caries and periodontal diseases. (25)

2.2.4. Other oral diseases

A higher prevalence in diabetic patients than non-diabetic is find in the following oral manifestations: fissured tongue, burning mouth syndrome, yellow discoloration of the tongue, ecchymosis or ulcers, oral lichen planus and caries (26,31).

Higher level of salivary glucose is found in diabetic patients which is a risk factor of oral candidiasis. (32)

2.3. Chronic and acute complications related with glycaemia in DM patients

Glycaemia varies throughout the day for everyone, this is a process totally physiologic. In the patients with DM, more importance is given to monitor their glycaemia, because of the lack of sensitivity or deficiency of insulin. This can lead to various acute or chronic complications depending on the situation.

2.3.1. Acute complications

2.3.1.1. Hypoglycaemia

Hypoglycaemia is defined as a blood sugar level of less than 70mg/dL in diabetic patient or as “all episodes of an abnormally low plasma glucose concentration that expose an individual to potential harm”. (28)

There are 3 different levels of hypoglycaemia (9,34):

- Level 1 mild hypoglycaemia: blood sugar levels between 70 mg/dL (3.9 mmol/L) and 54 mg/dL (3.0 mmol/L).
- Level 2 hypoglycaemia: blood sugar levels between 54 mg/dL (3.0 mmol/L) and 36 mg/dL (2.0 mmol/L).
- Level 3 severe hypoglycaemia: blood sugar levels below 36 mg/dL (2.0 mmol/L).

According to ADA, following the level of glycaemia we will find different symptoms like sweating, tremors, confusion, dizziness, headache, weakness, loss of consciousness coma or even death. It is important to note that the severity of the symptoms varies depending on individual factors, diabetes management, and treatment plans. Neuroglycopenic symptoms begin to appear in level 2, and in level 3 significant mental and physical changes require the help of another person.

2.3.1.2. Diabetic ketoacidosis complication

Diabetic ketoacidosis (DKA) is a serious complication that occurs in people with diabetes, especially T1D. The concentration of ketones in the blood increases, making the blood more acidic (venous pH less than 7.3) and an increase in the glycaemia of more than 250mg/dL. This occurs when the body is

unable to use glucose for energy due to a lack of insulin, causing it to break down fat and produce ketones as an alternative source of energy (9,35). According to ADA, symptoms of DKA include excessive thirst, frequent urination, nausea and vomiting, confusion, rapid and deep breathing, and fruity or sweet breath. Diabetic ketoacidosis is a medical emergency that requires urgent treatment to avoid life-threatening complications. (36,37)

2.3.1.3. Hyperosmolarity hyperglycaemic state

Hyperosmolar hyperglycaemic state (HHS) is a potentially life-threatening complication, when left untreated it can cause severe dehydration, seizures in many cases, a potential decrease or loss of consciousness, blood clotting issues and acute kidney injury or even kidney failure (35,38). HHS primarily occurs in people with T2D, especially the elderly. It is characterized by very high glycaemia (above 33.3 mmol/L or 600 mg/dL), by insulinopaenia (deficiency or insufficient levels of insulin in the bloodstream), high plasma osmolality (above 320 mOsm/Kg) and a significant absence of ketoacidosis (35,39).

According to ADA, “HHS is the most serious hyperglycaemic emergency in T2D patients”. The condition can progress slowly over days or weeks, and symptoms include excessive thirst, frequent urination, fatigue, muscle weakness, confusion, and seizures. Treatment of HHS includes rehydration to prevent dehydration, insulin to lower blood sugar levels, and administration of electrolytes to restore electrolyte balance. (36,39)

2.3.2. Chronic complications

2.3.2.1. Hyperglycaemic impacts on oral health

Advanced glycosylation end products (AGE) are formed when proteins and other molecules in the bloodstream become coated with excess glucose. Glycation occurs naturally in the body when glucose molecules bind to proteins and lipids. However, AGE formation can become excessive when blood glucose levels are consistently high, as in uncontrolled DM. AGE can accumulate in a variety of tissues and organs, activating immune cells and inducing inflammation. When bonded to its specific receptor (RAGE), it can causes perpetual microvascular damage and therefore aggravate periodontal disease. (24)

Moreover, DM can reduce the capacity of the innate (neutrophils and macrophages) and adaptive (T cells) immune system to respond against exogenous pathogens. This disfunction can lead to impaired clearance of bacteria and debris from wounds, chronic infections, and delayed wound healing. (25,40)

2.3.2.2. General health complications

As mentioned in section above, hyperglycaemia in diabetic patients has a direct impact on immune and vascular system leading to general complications. When uncontrolled or poorly controlled DM has 6 general complications in total in the human body mainly due to micro and macro vascular complications (17):

- Retinopathy.
- Neuropathy.
- Nephropathy.
- Cardiovascular diseases.
- Peripheral vascular diseases.
- Predictors of periodontal diseases and oral manifestations.

2.4. Background

Frederik G. Banting and John J.R. MacLeod received the Nobel Prize of Medicine in 1923 for the discovery of insulin (thanks to studies and work of many previous scientists). And still since these discoveries, DM is a chronic illness affecting severely public health (10). Insulin injection is not a cure for diabetes, it is a treatment.

Impact of sedentary lifestyle (lack of sports, high sugar food consumptions,...) increases considerably the number of T2D patients in the world (1,41). Furthermore, there has been a gradual increase in the incidence of Type 1 Diabetes since the 1950s, with these patients accounting for around 5 to 10% of all cases of diabetes (9,42). According to the World Health Organisation (WHO), T2D affects 95% of patient's diabetes. In 2019, it was reported that the worldwide population of individuals suffering from diabetes surpassed 463 million with projections indicating that number will rise to 700 million by 2030. (41)

Almost half of diabetic people are unaware they have diabetes, and 75% of them live in low or middle income countries (16).

2.5. General treatment for diabetes

2.5.1. General prevention

Nowadays, most important way to treat diabetes is to have a healthy diet and to perform regular sport activity. Purpose is to treat diabetes by restoring the carbohydrate metabolism to a normal state. For T1D patients there is a lack of insulin production, with a great monitoring of glycemia patient will inject insulin directly or use an insulin pump. It has been shown evidence that patients using pump injection had less risks of hypoglycaemia than using insulin injection therapy. (37) Continuous glucose monitoring has been demonstrated to be beneficial in diabetic patients, especially in T1D young patients (43).

In T2D patients, the purpose is to reduce glycemia, and to prevent long term complications. First management to prevent T2D or GD is to increase physical activity, have a healthy nutrition and lose weight whereas obesity and physical inactivity are risk factors for T2D (4,44).

The management of diabetic patients changes according to the type of diabetes, sex, age, how long their diabetes has been under control or not and if they have other chronic diseases. There is evidence of different diabetes prevalence following if diabetic patients are coming from urban or rural area and low or high income countries (41).

People with IFG and IGT should be monitored on a regular basis for the development of diabetes mellitus, and preventive measures can be taken to reduce the risk.

New tools for diabetic patients have been developed in the past few years, especially since covid pandemic like phone applications to control food and meals nutrients calculation at home directly. Some applications now directly establish an individual profile following personal patient’s data, and thus improve the metabolic control of diabetes. This new technology allows patients to have a better self-control of their diseases.

2.5.2. Diabetes medication

Here some examples of major medications other than insulin used to treat diabetes:

- Metformin is a medication helping to reduce glycaemia, by reducing glucose production from the liver, some studies state that it increases the body's sensitivity to insulin. This drug is commonly prescribed in patients with T2D. Side effect of metformin seems to be gastrointestinal disturbances (diarrhea, nausea,..) and in rare cases lactic acidosis (excess of lactic acid in the blood). (45)
- Sulfonylureas are oral medications used in patients with T2D by increasing insulin production in the pancreas. A common side effect of sulfonylureas is hypoglycaemia. (46)
- DPP-4 inhibitors are a class of oral medications used in the management of T2D patients. They inhibit an enzyme call "dipeptidyl peptidase-4", which results in increased levels of incretin hormones. These hormones help regulate blood sugar levels by stimulating insulin release and reducing glucose production by the liver. (47)

2.6. Research question

What relevant data are used by the dentists in the management of the diabetic patients?

3. OBJECTIVES

Principal objective:

- Describe oral health complications linked with diabetic patients.

Specific objectives:

- Put in evidence the bidirectional relationship between periodontitis and diabetes.
- Describe intra oral biomarker used the diagnostic of diabetes.

4. MATERIAL AND METHODS

4.1. Source of information and eligibility criteria.

To realize this review, an electronic data collection has been collected amongst the following platform: Medline complete with the key words “dentistry”, “oral health”, “diabetes mellitus”, “diabetic patient”, “periodontitis”, “oral manifestation”, “management”, “glycemia”, “oral lesions”, “diabetes complications” , “xerostomia”, “oral candidiasis”, “prevalence”, “identification”, “impaired glucose metabolism”, “association”, “bidirectional”, “salivary biomarker”, “relationship”, “correlation”, ”salivary Alpha-2 Macroglobulin”, “salivary glucose”, “HbA1c” and “Type 2 diabetes”.

The purpose was to collect the maximum of information regarding the definition of DM and its associated manifestations on the human body and oral cavity. Then to find the latest data being used in the management of diabetic patients in dental offices. The relevant references of the scientific articles were also collected in the data collection.

The most relevant articles were reviewed manually and selected based following the inclusion and exclusion criteria shown in **Table 4.** and the search strategy in **Table 5.**

The literature search for this study was conducted using Boolean methods to generate an accurate and comprehensive search strategy.

Table 4. Inclusion and extrusion criteria.

Inclusion criteria	Exclusion criteria
○ Dated of 20 years or less. ○ Written in English, French or Spanish. ○ Full text available. ○ Clinical human studies	○ Articles dated before 2012. ○ Studies related to diabetic patients with chronic or immunosuppressive diseases (such as cancer, HIV, hepatitis...). ○ Animal studies

4.2. Literature Search strategy

Table 5. Summary of search strategy

Database	Search strategy	Number of results obtained	Research date
Medline	(Diabetes mellitus) AND (Oral health) AND (Oral manifestations) AND (Periodontitis) (From 2013 to 2023)	13	02/03/2023
	(Diabetes mellitus) AND (Oral health) AND (Oral manifestations) AND (xerostomia) (From 2013 to 2023)	9	02/03/2023
	(Diabetes mellitus) AND (Oral candidiasis) AND (Prevalence or Identification) (From 2013 to 2023)	28	03/03/23
	(Periodontitis) and ("impaired glucose metabolism") (From 2013 to 2023)	8	03/03/23
	("Diabetes mellitus") AND ("Oral health") AND (Periodontitis) AND (Association) (From 2013 to 2023)	111	03/03/23
	((periodontitis OR "periodontal disease" OR "gum disease") AND (diabetes OR "diabetic patients") AND "bidirectional") NOT "animal" NOT (Review) (From 2013 to 2023)	68	03/03/23
	("oral biomarkers" OR "intraoral biomarkers" OR "salivary biomarkers") AND (diabetes OR "diabetes mellitus") NOT animal (From 2013 to 2023)	31	03/03/23
	(Relationship OR Association OR Correlation) AND (Salivary Alpha-2 Macroglobulin OR Salivary A2MG OR Salivary glucose) AND (HbA1c OR Type 2 diabetes OR Diabetes Mellitus) AND (Cross-sectional study OR case-control study) (From 2013 to 2023)	45	03/03/23

5. RESULTS

This graduation project was conducted based on 313 articles on Medline platform in total. According to the different inclusion and exclusion criteria, and assessment of keywords, titles, abstracts we have selected 11 articles. **(Figure 1.)**

Among this selection we can find:

(2) Systematic reviews.

(5) Cross sectional studies.

(3) Case control study.

(1) Randomized clinical trial.

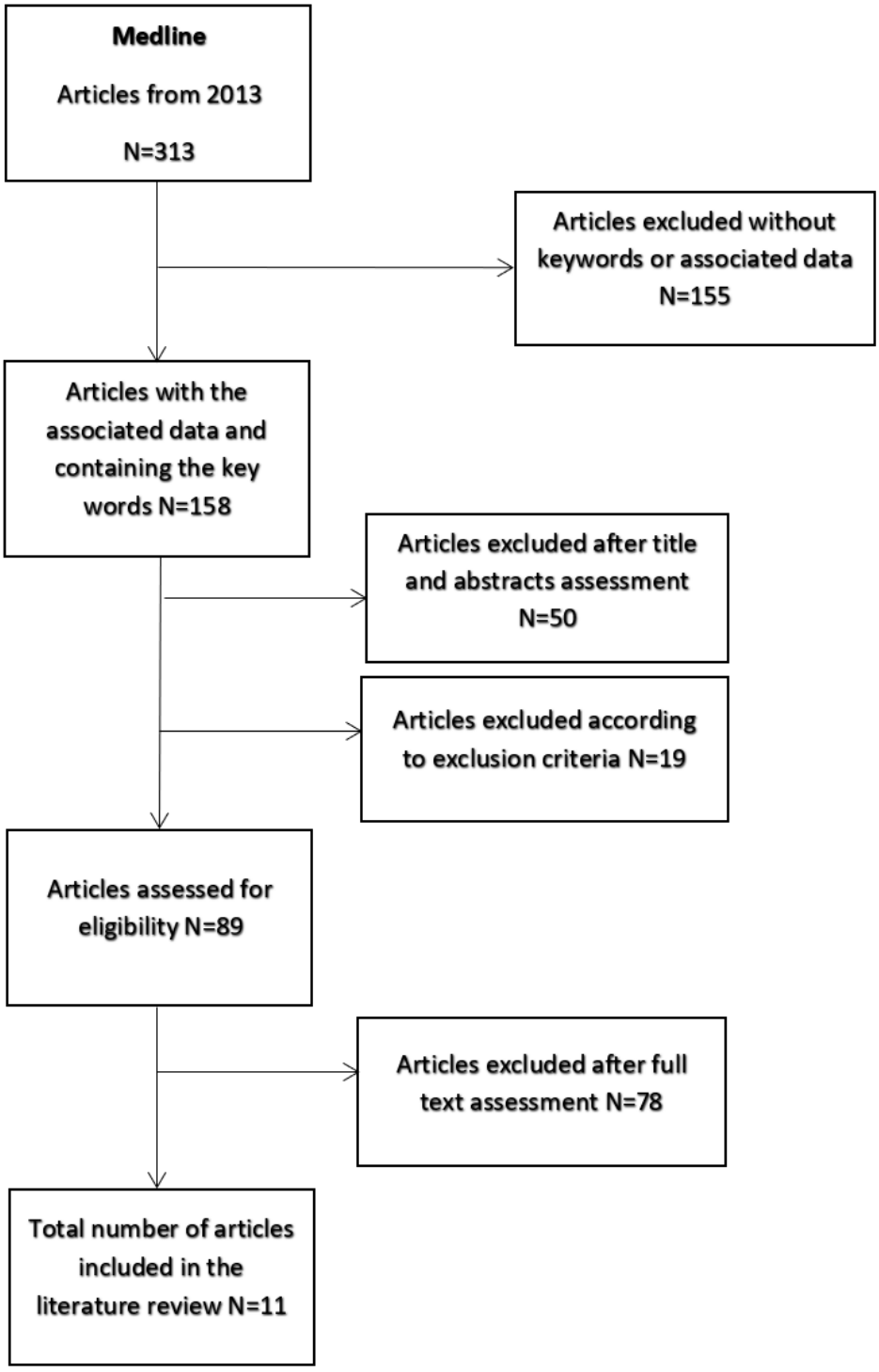

Figure 1. Prima flow diagram for study selection

Table 6. Results of principal objective: Oral health complications linked with diabetic patients.

Study, year	*Type of study*	*Evolution time*	*Sample size*	*Criteria for diabetes diagnosis*	*Methods used to identify the manifestation.*	*Results and association risk*
Gustavo G. Nascimento et al, 2018 (48)	Systematic review (13 articles included in the analysis).	8 to 20 months With a mean of 4.8 years for the 13 studies	N= 49 262 Including 3 197 diabetic patients.	HbA1c ≥ 6% and use of current medication (1 study) HbA1c ≥6.5% (1study). HbA1c ≥ 7% (2 studies). HbA1c ≥ 8.6% (1 study). HbA1c ≥ 8.4–9.6% for controlled diabetes and HbA1c ≥ 10.7% for uncontrolled diabetes (1 study). HbA1c ≤ 8.9% for controlled diabetes and HbA1c ≥ 9.0% for uncontrolled diabetes (1 study). FPG ≥ 126 mg/dL (2 studies).	Periodontitis identification: Self-report questionnaire (1 study). Detection of proximal bone loss using radiographs (1 study). Clinical examination for 11 studies (9 have chosen the whole mouth and 2 dental index) using AL, periodontal probing depth (PPD) and community periodontal index score (CPI): ○ AL and PPD (4 studies) ○ AL only (2 studies) ○ PPD only (1 study)	Crude data: Estimated in relative risk (RR) RR= 1.70% with a confidence interval of 1.3 to 2.3 (95%). After adjustments: RR=1.80% with a confidence interval (CI) of 1.3 to 2.8 (95%). DM increased risk of incidence and progression of periodontitis.

				Clinical examination (3 studies). Diagnosis is performed by clinical exploration (1 study).	○ CPI > 3 (4 studies)	
Elisabet Mauri-Obradors et al, 2017 (49)	Systematic review (19 articles included in the analysis: 4 longitudinal studies and 15 cross-sectional studies).	N/A	N= 3 712 including 2 084 diabetic patients	N/A	Periodontal disease. Periapical lesion. Xerostomia. Taste alteration. Caries (root caries included) Mucosal lesions. Method to identify those oral manifestations had not been described.	Out of the 19 studies analysed, 14 studies found a positive association between DM and oral manifestations: 2 studies found association with periodontal disease and 3 studies with periapical lesion. 4 studies found higher incidence of xerostomia and 1 study found higher incidence in taste alterations in DM group. Regarding caries, 40% (2 studies) found a positive association with DM and 60% (3 studies) did not. Mucosal lesions 50 % (1 study for oral candidiasis and 1 study for oral lichen planus) found an association with DM while 50% (2 studies) did not. 5 studies did not find significant differences between the diabetic and healthy control group.

Eduardo Montero et al, 2019 (50)	Cross-sectional study	N/A	N= 4222 patients. Including 95 diabetic patients and 373 prediabetic patients.	Fasting plasma glucose concentration: Normal glucose level: FPG < 100mg/dL Prediabetes: FPG comprises between 100 and 126mg/dL Diabetes: FPG > 126mg/dL or prior diagnosis of diabetes or taking medication for diabetes.	Periodontitis identification: Periodontal status is assessed by (CPI) and clinical attachment levels (CAL).	Patients with a CPI 4 were significantly associated with DM: Estimated in odds ratio (OR) OR= 3.97 with a CI of 1.24 to 12.68 (95%) for patients younger than 45 years old. OR=1.69 with a CI of 0.99 to 2.90 (95%) for patients older than 45 years old. In women subjects the presence of a CPI of 4 is not significantly associated with altered glucose levels. In men subjects, presence of a CPI of 4 increased in subjects with DM: OR = 1.88 with a CI of 1.12 to 3.16 (95%). No significant association was found for IFG.
Halimi et al, (2018) (23)	Case control study	N/A	N=122 90 women and 32 men in total.	Diagnostic based on “the 2020 Diagnostic Criteria” of ADA.	Oral candidiasis identification: Two swabs of the tongue are obtained by mouth.	Oral candidiasis is more frequent in T2D patients (51.85%) than in non-diabetic patients (31.70%). No significant association between level of HbA1c and

	First group is composed of 81 T2D patients with 60 women and 21 men. Control group is composed of 41 non-diabetic with 30 women and 11 men.	One swap was cultured in Sabrodextrose agar medium, to determine presence or not of Oral candidiasis: Using Colony Forming units (CFU): If CFU>5 presence of oral candidiasis IF CFU<5 no presence of oral candidiasis. The second swab was cultured on chromium-agar medium (CHROMagar) to identify the type of oral candidiasis. Blood samples were taken 8-10 hours before to determinate levels of HbA1c, fasting blood sugar (FBS), level of interferon-gamma cytokines (IFN-γ) and Interleukin 10 (IL-10).	FBS in the development of oral candidiasis in both groups. *C. Albicans* has the highest prevalence in both groups (45% in T2D group and 69% in the control group). An increase of (IL-10) increases prevalence of oral candidiasis in diabetic patients (OR=1.40). A decrease of (IFN-γ) increase prevalence of oral candidiasis in diabetic patients (OR=0.94). Age and sex have not significant impact in oral candidiasis development.

Mohammadi F et al, 2016 **(25)**	Case control study	From June 2014 to September 2015.	N=106 subjects. First group is composed of 58 diabetic patients. And a control group composed of 48 non-diabetic patients.	N/A	Oral candidiasis identification: Swabs taken from the mouth of each subject and cultured on Sabouraud dextrose agar medium. PH and salivary glucose were collected to perform measurements.	Frequency of *Candida* species is higher in diabetic group (55%) than in control group (35.5%). *Candida albicans* was the most frequently identified species in both groups, with a prevalence of 43.1% in the diabetic group and 27% in the non-diabetic group. There is a reduction of salivary pH (6.52 ± 0.48) in the diabetic group in comparison with the non-diabetic group (6.87±0.29). A lower salivary glucose level was observed in the group with less than 50 colonies (2.25±0.44) compared to the group with more than 50 colonies (2.78±0.54). The prevalence of dry mouth was 33.33% in the group with less than 50 colonies, whereas it was 69.4% in the group with more than 50 colonies.

Table 7. Results of first specific objective: Bidirectional relationship between periodontitis and diabetes

Study, year	*Type of study*	*Evolution time*	*Sample size*	*Inclusion criteria*	*Parameters recorded in the study*	*Results*
Ravishankar Lingesha Telgi et al., 2017(51)	Randomized controlled clinical trial	3 months	60 subjects 3 groups of 20 patients each: Group A (1 scaling, mouthwash, and brushing) Group B (mouthwash 1 time each day and brushing 2 times a day) Group C (control group) were asked to brush 2 times a day.	Patients controlled with oral hypoglycaemic agent diagnosed with T2D. Mild to moderate periodontitis.	Assessment of PPD, level of HbA1c, FBS, gingival index (GI) and plaque index (PI). Medication history was noted at the beginning of the study and after 3 months of treatment.	The mean differences between PPD, FBS, HbA1c, GI, and PI in groups A and B were statistically significant ($P < 0.001$) and Group C does not show differences on theses parameters ($P=0.078$). Mean standard deviation is reduced in group A (0.58±0.27), group B (0.25±0.14) and group C (0.004±0.12). Group A showed a reduction from 5.05±0.7 PPD and 2.16±0.46 GI score at baseline to 4.59±0.72 PPD and 1.59±0.18 GI score after 3-month intervention. Group C show a PPD of 5.05±0.69 and GI score of 2.22±1.11 at baseline to a PPD of 5.03±0.69 and GI score of 2.19±1.08 after 3-month intervention.

						GI and frequency of drug administration are independently associated with HbA1c level.
Basant M. Mehriz et al, 2021 (52)	Cross sectional study	For 6 years: Oral examination was performed from 1988 to 1994 in two phases.	N= 13 000 patients Mean age 43.8 years old. 47.5% men. 52.5% women.	Patients with natural teeth from the “Third United states National Health and Nutrition Examination Survey” from 1988 to 1994	Periodontitis was defined as: Moderate (> 4mm AL or 5mm PPD in 2 or more mesial sites Severe (> 6mm AL in 2 or more mesial sites and PPD > 5mm in 1 or more mesial site. DM defined as FPG ≥ 126mg/dL, or HbA1c ≥ 6.5% or the use of antihyperglycemic medications.	12.7% of sample has periodontitis. 9.2% of sample had DM. DM prevalence is higher in patients with severe periodontitis (26%) and lowest with no periodontitis (7.7%). This study dressed a multivariable-adjusted logistic regression model: Moderate or severe periodontitis are associated with increased odds of developed DM: OR=1.66 with a CI of 1.43 to 1.99 (95%). Severe periodontitis odds of DM: OR=2.31, and (95%) CI 1.72 to 3.11, p < 0.001), compared to individuals without periodontitis. Moderate periodontitis odds of DM: OR=1.54 and (95%) CI 1.30 to 1.82 with p < 0.001), compared to individuals without periodontitis.

SKM Azizul Islam et al, 2015 (53)	Cross sectional study	2008-2010	N= 19 122 subjects with 8 248 men and 10 874 women.	Participants ≥ 20 years old From Korea National Health and Nutritional Examination Surveys.	Periodontitis with a CPI ≥ 3, insulin resistance (IR), homeostasis model assessment of insulin resistance (HOMA-IR) and β-cell function (HOMA-β). IFG, FPG (considered diabetics if patient got FPG > 126mg/dL), HbA1c level, body mass index, insulin measurements. Arterial pressure, smoker or not.	31.3% of total sample present periodontitis (CPI ≥ code 3). Level of FPG HbA1c got higher means values in subject with periodontitis than without. Prevalence of IFG in patient with periodontitis are 28.5 % and in patient without periodontitis are 17.7%. This study used different multivariable logistic regression analysis adjusted with sex, age and body mass index: • Study shows significant association between periodontitis and diabetes: OR=1.445 with a CI (95%) of 1.307 to 1.597. • Study shows significant association between periodontitis and IFG: OR=1.302 with a CI (95%) of 1.199 to 1.413. • Study shows significant association between periodontitis and HOMA-β:

			(95% with a CI of -10.279 to -5.110, p<0.001). • Study shows significant association between periodontitis and HOMA-IR only when age, sex, body mass index, systolic blood pressure and serum total cholesterol parameters were adjusted: (95% CI, -0.027-0.001, p<0.05)

Table 8. Results of second specific objective: Studies investigating intraoral biomarkers for the diagnosis of diabetes.

Study, year	*Type of study*	*Sample size*	*Inclusion criteria*	*Parameters recorded in the study*	*Results*
Vanshika Rastogi et al, 2019 (54)	Cross-sectional study	N= 87 subjects	Patients with T2D without hepatic or inflammatory diseases of oral cavity and body.	Levels of salivary alpha-2-macroglobulin (A2MG), HbA1c, FPG and postprandial blood sugar (FPBS), and serum creatinine were compared. A2MG were evaluated with enzyme-linked immunosorbent assay	Positive association between salivary levels of A2MG and blood levels of HbA1c in patients withT2D. The linear correlation coefficient between these two variables is: 0.977 ($p<0.001$) Significant correlations were also observed between mean values of FPG and FPBS, serum creatinine, and salivary A2MG in diabetic subjects.
Tsung-Ju Chung et al. 2016 (55)	Cross-sectional study	N= 91	Patients with T2D.	Level of salivary A2MG, plasma A2MG, FPG, HbA1c and periodontal condition.	A2MG salivary levels are statistically associated positively with plasma A2MG levels, FPG, HbA1c and periodontitis condition. Correlation between salivary A2MG and Hb1Ac $r=0.443$ ($p= 0.006$) $p < 0.001$
Vineet Gupta et al. 2020 (56)	Case control study	N= 90 45 with DM 45 healthy subjects (control group)	Patients diagnosed with DM and healthy patients. Age comprises between 25 and 70 years old	Salivary and blood glucose level. Measures are done every 8 hours fasting and 2 hours after meal.	Mean salivary glucose of 1.002mg/dL in patients with blood glucose level ranged from 100 to 280mg/dL. Mean salivary glucose of 2.31mg/dL in patients with glucose level ranged from 180 to 440mg/dL.

6. DISCUSSION

To address our principal objective, we included two systematic reviews, two case-control studies, and one cross-sectional study, each study discussed the prevalence and incidence of diabetes patients developing oral complications. Regarding the first specific objective about the bidirectional relationship between periodontitis and diabetes, we have included two cross-sectional studies and one randomized controlled clinical trial study, purpose of this objective was to show periodontitis as a risk factor of DM. Lastly, our second specific objective about the description of intra oral biomarker used in the diagnostic of diabetes is composed of two cross-sectional studies and one case control study.

6.1. Principal objective: Oral manifestations associated with diabetic patients

6.1.1. Diabetes as a risk factor for periodontitis and tooth lesions.

A substantial connection between periodontitis and diabetes mellitus (DM) was identified. In the 13 studies reviewed by Gustavo G. Nascimento et al., a significant heterogeneity was found, and after making correct adjustments, the review estimates that DM increases incidence or progression risk of periodontitis by 80%. This positive association is further supported by the work of Elisabet Mauri-Obradors et al. who found a positive association between DM and development of oral manifestations in 14 of the articles reviewed. This previous study also identified two other articles that observed a positive association between caries and DM and three studies which did not find any association. Lastly five studies did not find significant differences between diabetic group and healthy control group. In the study by Eduardo Montero et al. patients younger than 45 years old with periodontitis had a higher risk of developing diabetes compared to older patients. Not only presence of periodontitis has been identified but severe form of periodontal disease are important factors to consider. A significant absence of association between DM and periodontal disease in female subjects is found. Prediabetes in Eduardo Montero et al. study did not identify IFG as risk factor of periodontitis.

A possible reason explaining the inconsistency of non-association between caries and DM could be the dietary changes that diabetic patients have to make, by consuming a less carbohydrate-rich diet. However, it should be noted that other factors such as glycaemic control, quality of saliva influenced by DM and oral hygiene may also play a role in the relationship between caries and diabetes. In addition, reduced vascularity and limited oxygen supply caused by hyperglycaemia can impair wound healing and make individuals more susceptible to infections caused by anaerobic bacteria.

Another explanation for the absence of significant association could be attributed to variations in study design, population characteristics, or the fact that certain oral health manifestations may not be directly associated with DM, but rather with other co-existing factors or conditions not mentioned in the review.

These result indicate that the strength of the association between DM and periodontal disease may vary depending on factors such as age. These data highlight the aggressiveness of DM and the importance of early detection and treatment of diabetes, especially in younger patients with periodontal disease. Moreover, the lack of positive association between IFG patients and periodontal disease emphasizes the importance of early diagnosis prior on the onset of the disease. The lack of significant association between DM and periodontal disease observed in female subjects in the study conducted by Montero et al. may be attributed to the small sample size of women with DM (7 subjects). In contrast, the study by Elisabet Mauri-Obradors et al. found a greater diversity in male and female ratio and a positive association between DM and periodontal disease.
Further investigations are needed to understand the underlying mechanisms of this controversial relationship.

6.1.2. Association between diabetes and oral candidiasis

A higher prevalence of oral candidiasis in diabetic patients is observed compared to non-diabetic individuals. Halimi et al. and Mohammadi et al. found similar results: higher presence of oral candidiasis in diabetic patients than in non-diabetic group. In both studies, prevalence of *Candida species* is higher in diabetic patients in comparison with non-diabetic group while *Candida albicans* was identified as the most common species in both diabetic and non-diabetic

groups. No significant association was observed between levels of HbA1c and FPG in the development of oral candidiasis in both diabetic and non-diabetic group. The study also found no significant impact of age and sex on oral candidiasis development.

A reason explaining the higher prevalence of *Candida species* in diabetic patients than in non-diabetic group, could be due to several factors such as immune or vascularity impairment and higher glucose level. Both studies highlight the need for continued monitoring and management of oral health in diabetic patients to prevent the development or exacerbation of oral candidiasis. Variances in patient groups and methods of administration could account for the different outcomes and explain the non-association observed between HbA1c and FPG levels and development of oral candidiasis.

6.1.3. Salivary changes associated with diabetes

Several studies have reported an association between DM and xerostomia. Elisabet Mauri-Obradors et al. and Mohammadi et al. observed that xerostomia is associated with DM. Mohammadi et al. reported a reduction in salivary pH in the diabetic group compared to the non-diabetic group. The study also found a higher prevalence of dry mouth and higher salivary glucose in individuals with more than 50 colonies of *Candida* compared with the group with less than 50 colonies.

Both studies suggest that there is an association between DM and dry mouth, as well as changes in salivary glucose levels and pH, which may contribute to the development of oral health problems. These changes in saliva may lead to alterations in oral microbiota, which could play a role in the development of gingivitis, periodontitis and oral candidiasis infections in diabetic patients.

Overall, the five studies we reviewed show that the consequences of DM on oral health are interrelated and may exacerbate each other, creating a vicious cycle impacting severely oral health. Those results highlight the need for a holistic approach in the management of oral health in patients with DM presenting these manifestations.

6.2. Bidirectional relation between diabetes and periodontitis.

The three selected studies observed that periodontitis could be a risk factor for DM. On the randomized controlled clinical trial study, Ravishankar Lingesha Telgi et al. found among T2D patients that a three-month intervention of scaling, mouthwash and brushing had significant effect on lowering HbA1c level in comparison with control group. Results suggest that poor oral hygiene, as reflected with an increase GI score, is associated with higher HbA1c levels. Furthermore, Ravishankar Lingesha Telgi et al. study has investigated only following “mild to moderate” periodontitis in T2D patients, in response to this limitation Basant M. Mehriz et al. demonstrated an increase in the OR of developing DM in patients with moderate or severe periodontitis. The study conducted by SKM Azizul Islam et al. found a significant association of periodontitis with the IFG level and HOMA-β (reflecting pancreatic β cell function). No significant association were found between periodontitis and HOMA-IR (reflecting insulin resistance).

These results imply that any intervention aimed to reduce periodontal inflammation have a positive impact on glycaemic control of patients with diabetes. Importance of patient involvement in the management of his own systemic disease may be crucial. Another possible explanation for this association is that individuals with DM who take better care of their oral health may also be more attentive to their overall health needs, including their glycaemic control. Results suggest that periodontitis contribute to impaired glucose metabolism in DM patients, through its effect on pancreatic β cell function. An explanation of the non-association between periodontitis and HOMA-IR could be that insulin resistance is not directly linked with periodontitis. More investigations are needed to confirm the existence or not of correlation with insulin resistance and pancreatic β cell function.

It is important to note that the study conducted by Ravishankar Lingesha Telgi et al. has some limitations, such as a small sample size (60 subjects) and a three-month follow-up period. As a result, larger sample sizes and longer follow-up periods may be required in future studies to confirm these findings and determine

the long-term benefits of periodontal therapy in improving glycaemic control in T2D patients. Azizul Islam et al. and Basant M. Mehriz et al. are limited by their cross-sectional design, they measure variables at a single point in time and do not establish causality or temporal relationships between the different variables.

6.3. Intraoral biomarker for diagnosis of diabetes.

A positive association have been found between DM and salivary glucose or salivary alpha-2-macroglobulin (A2MG).

Vineet Gupta et al. observed a higher mean salivary glucose in patients with higher blood glucose levels and a lower mean salivary glucose in patients with lower blood glucose levels. On both cross-sectional studies, Vanshika Rastogi et al. and Tsung-Ju Chung et al. found a positive association between salivary levels of A2MG and HbA1c in patients with T2D. Salivary A2MG could be used as a non-invasive method to monitor glycaemia over the last 4 months, instead of collecting blood sample.

Study emphasizes the use of saliva as a tool to evaluate glycaemia in patients with T2D. These findings suggest that measuring salivary glucose levels could potentially be a non-invasive method for diagnosing and monitoring DM. However, it is important to note that saliva and blood are different biological medium, so the correlation is not always linear and may depend on many other factors. The results of the three studies should be interpreted with caution and require further validation before they can be used clinically.

7. CONCLUSIONS

For our principal objective, dentist must be able to recognize typical oral lesions related to DM and suspect undiagnosed DM. Treatment should be tailored according to the type of diabetes and its control status, with particular attention to periodontal health, xerostomia, and oral candidiasis. Healthcare professionals should receive thorough training to improve interdisciplinary collaboration and provide holistic care.

Regarding our second objective, periodontitis and DM have a bidirectional relationship, emphasizing the importance of patient communication and follow-up. The goal for health professionals is to make scientific knowledge available to

the patient through appropriate communication to let him understand that he is the primary actor in his management of DM.

An efficient way to manage diabetic patients, is to perform an early diagnosis. The third objective give information about new non-invasive procedures to diagnose and monitor DM, putting in evidence a link between glycaemia and salivary glucose level. Further investigations are necessary before this method can be used clinically.

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