

## Interrelation between diabetes mellitus and periodontal disease: an integrative review

### Inter-relação entre diabetes mellitus e doença periodontal: uma revisão integrativa

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**RESUMO | INTRODUÇÃO:** Nos casos onde existe uma associação de duas ou mais doenças, melhorar o bem-estar e a qualidade de vida do indivíduo torna-se algo mais complexo, principalmente quando estas doenças possuem uma relação bidirecional, como é observado entre a diabetes mellitus e a doença periodontal. **OBJETIVO:** O presente estudo tem por objetivo, revisar a literatura sobre a relação entre o Diabetes Mellitus e a Doença Periodontal, identificando no que lhe diz respeito os principais aspectos e características patognomônicas. **CONCLUSÃO:** Conclui-se que devido às controvérsias encontradas na literatura sobre a inter-relação do diabetes mellitus e a doença periodontal, são necessários maiores estudos para uma maior compreensão sobre o tema; podendo afirmar que a abordagem interdisciplinar é de grande importância para que o paciente venha a dispor de uma melhor qualidade de vida.

**PALAVRAS-CHAVE:** Diabetes mellitus; Doença periodontal; Interrelação.

**ABSTRACT | INTRODUCTION:** In cases where there is an association of two or more diseases, it's complex to improve individual's well-being and quality of life, especially when these diseases have a bidirectional relation, as observed between diabetes mellitus and periodontal disease. **AIM:** The present study aims to review the literature on the relation between Diabetes Mellitus and Periodontal Disease, identifying the main aspects and pathognomonic characteristics. **CONCLUSION:** Due to the exposed in the literature on the interrelation of diabetes mellitus and periodontal disease, further studies are needed for a better understanding of the subject, knowing that the interdisciplinary approach is very important for the patient to have a better quality of life

**KEYWORDS:** Diabetes mellitus; Periodontal disease; Interrelation.

## Introduction

Diabetes Mellitus (DM) and periodontitis show high prevalence rates in the population and their interrelation represents an example of how a systemic disease may lead an oral infection<sup>1</sup>. It is understood that DM is a risk factor for the occurrence and severity of periodontal disease and an important factor for this relation is the glycemic index<sup>2</sup>. In parallel, periodontitis can have a significant impact on diabetes, making glycemic control difficult. Thus, these two diseases demonstrate a bidirectional pathway, which allows considerable changes in the individual's systemic condition<sup>3</sup>.

Periodontal Disease (PD) is an inflammation derived from the interaction between the accumulation of dental biofilm and bacterial metabolites generated on the margin of the gingiva, which give rise to an immune response of the host<sup>4</sup>. The activation of the host's immune system corroborates with the tissue destruction, causing the synthesis and release of cytokines, inflammatory mediators and metalloproteinases<sup>5</sup>. The periodontal destruction observed in periodontitis depends on the balance between the virulence of the local biofilm and the host's immune response<sup>6</sup>.

Periodontal disease is characterized by clinical attachment loss, represented by root cementum, periodontal ligament and alveolar bone loss. Prior to PD, gingivitis can be observed and the treatment of these two clinical conditions involves the recovery of health status and the maintenance of periodontal structures in the long term<sup>7</sup>. The manifestation of the disease varies among the individuals, since it is directly related to the response of the host to the microbial challenge<sup>8</sup>. Generalized severe periodontitis can be diagnosed in about 5% to 20% of any population, while mild to moderate periodontitis affects most adults<sup>9</sup>.

The association between PD and DM is related to several factors, such as individual susceptibility, age, glycemic control, duration of diabetes, oral cavity care and behavioral habits. Even with the extensive study on the relation between these two diseases, it is important to note that most investigations considered only oral health status measurements obtained through direct clinical observations, without taking

into account the self-perception of the individual<sup>10</sup>. On the other hand, it has been considered that self-perception in oral health, although subjective, is an additional measure, in which it contributes to the evaluation of general health care; in turn, these subjective factors seek to assess the impact of health on the quality of life of the population<sup>11</sup>.

The present study aims to review the literature about the relation between Diabetes Mellitus and Periodontal Disease, identifying oral manifestations of Diabetes Mellitus, as well as systemic health repercussions of periodontitis.

## Literature Review

### Selection of Studies

This literature review was conducted using the following databases: Pubmed (<https://www.ncbi.nlm.nih.gov/pubmed>), Scielo (<http://www.scielo.org/php/index.php>). The keywords for the textual search were: Diabetes Mellitus; Periodontal Diseases; Interrelation. The inclusion criteria were: Literature that covers the subject under study, Literature of the last years, in which the period from 1993 to 2018 is involved; English and Portuguese Language, laboratory and clinical studies and systematic review. The exclusion criteria were: literature review, letter to the editor, opinion article, literature duplicated in databases and literature that did not address the variables under study.

### Diabetes Mellitus

Diabetes Mellitus is a disease as old as humanity itself; in Egyptian medical documents, the Ebers papyrus of 1550 BC had already referred to a disease which was characterized by the excessive elimination of urine. This symptom was found in individuals susceptible to the disease, resembles draining water through a siphon. The sweet taste of urine, compared to honey, complemented its denomination like diabetes mellitus<sup>12</sup>.

It is a disease that affects the metabolism of carbohydrates, lipids and proteins, with hyperglycemia being the main characteristic,

followed by a set of signs, which include: polydipsia, polyuria and polyphagia. Such symptoms are consequences of discontinuation of homeostasis and change in glucose metabolism. Diabetes produces changes in micro and macro vascular circulation. These changes are linked to the development of five classic chronic complications according to the lack of control of the disease: nephropathy, retinopathy, neuropathy, cardiovascular complications and changes in wound healing<sup>13</sup>. PD is considered the sixth most important complication<sup>14</sup>.

### **Epidemiological Aspects**

DM has a big dissemination and is considered a public health problem in developed and developing countries, because it's a disease that has a great prevalence in the world population, with increasing occurrence, related to chronic complications, reduction of useful life, increase of mortality and high individual and social costs<sup>15</sup>. Amidst many reasons for the high number of people with diabetes in the population, it can be highlighted: urbanism, industrialization, sedentary, inadequate eating habits and substantial weight gains. Obesity is considered the main risk factor for the occurrence of DM<sup>16</sup>.

### **Concept**

The term DM includes a group of multiple cause diseases that are characterized by hyperglycemia, followed by the deficiency or inability of the insulin to perform its proper functions. The beta cells by the pancreas are responsible for synthesizing and secreting the insulin hormone, which regulates blood glucose levels. In the long term, hyperglycemia causes damage, loss of function, and failure of several organs, especially the kidneys, eyes, nerves, heart and blood vessels<sup>17</sup>.

### **Ranking**

The classification of DM includes two main types of disease, type 1 and 2, besides gestational. Type 1 DM usually affects children and young people and is characterized by a lack of insulin, followed by autoimmune destruction of beta cells, necessitating hormone replacement for survival. Type 2 DM occurs more in adults, accounting for 90% of the world's cases, it is a metabolic disorder characterized by

high blood glucose, insulin resistance and relative lack of insulin<sup>18</sup>.

### **Diagnosis**

Type 1 DM is a slowly evolving disease that persists for years in a preclinical phase. In the period of manifestation there is the presence of hyperglycemia and ketoacidosis, characterized by the presence of ketone bodies in the urine<sup>19</sup>.

Type 2 DM is caused by insulin resistance and, most of the time, manifesting in individuals over 40 years of age. The pancreas secretes insulin normally, but there is a lot of insulin and glucose in the blood and cells with low glucose<sup>20</sup>.

The classic clinical signs and symptoms of diabetes include polyuria, nocturia, polydipsia and polyphagia, among other symptoms. The individual with type 1 DM is almost always lean, with recent and involuntary weight loss, while type 2 is usually overweight. Type 2 DM can manifest consequences of its chronic complications, such as myocardial infarction and retinopathy<sup>21</sup>.

### **Chronic Complications**

Deficiency in insulin secretion and reduction of its action in target tissue are changes that result in hyperglycemia and other metabolic disorders that, if not corrected, cause an evolution of DM, reaching chronic stages. The most widely used way to evaluate glycemic or metabolic control of DM is glycosylated hemoglobin (GAL), which expresses the average glycemic levels of the one or four months prior to blood collection. Among the main chronic complications are microangiopathy and neuropathy. The common cause of all is chronic hyperglycemia that causes glycosylation of proteins that make up structures of tissues and organs along with functional disorders<sup>22</sup>.

### **Complications on the oral cavity**

The oral cavity of people with DM shows favorable conditions for the occurrence of a series of non-specific complications, which may compromise their quality of life. Considering the complicating potential of individuals with inadequate metabolic controls,

the participation of the dentist in the assessment and follow-up team is important. Among these changes in the oral cavity are periodontal disease, xerostomia, frequent abscesses, opportunistic germ infections, enamel hypocalcification, among others. These disorders do not compromise the survival of diabetic individuals, but may interfere with quality of life, hinders metabolic control and worse other chronic complications<sup>23</sup>.

### Periodontal Disease

Periodontal disease is a chronic bacterial infection, characterized by the host's rapid inflammatory response to microorganism's challenge, which affects tooth-bearing tissues such as the gingiva, periodontal ligament, cement and alveolar bone. This infection influences the occurrence of events in other parts of the body, creating the communication of the oral infection with other systemic diseases<sup>24</sup>. Some culture methods have determined that approximately 500 species of bacteria are present in the oral cavity, of which approximately 415 are present in the subgingival biofilm, in commensal conditions. For periodontal disease to develop in an

individual, an imbalance occurs in the homeostasis of the microenvironment due to the presence of some factors such as genetic factors, environmental factors and periodontal pathogens, among which we can highlight: *Porphyromonasgingivalis*, *Aggregatibacter actinomycetemcomitans*, *Treponemadenticola* and *Tannerella forsythia*<sup>25</sup>.

Periodontitis is a pathology that is characterized by clinical attachment loss, where the periodontal tissues are affected by an inflammatory process<sup>26</sup>, compromising the periodontal insertion. Among the most common signs and symptoms are: flushing, pain, edema, local temperature increase and the presence of an inflammatory process<sup>27</sup>.

### Classification of the Periodontal Diseases

It is known that periodontal disease can present itself in various ways according to involvement of the periodontal tissues. There has been great difficulty over the years to attempt to group and order periodontal diseases into classes, but today there is a widely used classification as described in Chart 1.

Chart 1. Main periodontal diseases, author / year, kind of study, definition (to be continued)

Main Periodontal Diseases	Author / Year	Kind of study	Definition
Gingivitis	Chapple et al., 2018 <sup>58</sup> Murakami et al., 2018 <sup>59</sup>	Literature review	The universal features of these gingival conditions include: clinical signs and symptoms of inflammation that are confined to the free and attached gingiva and do not extend beyond the mucogingival junction; reversibility of the inflammation by disrupting/removing the biofilm; the presence of a high bacterial plaque burden to initiate and/or exacerbate the severity of the lesion (although this varies among individuals); and stable (i.e., unchanging) attachment levels on a periodontium, which may or may not have experienced a loss of attachment or alveolar bone.
Chronic periodontitis	Papapanou et al., 2018 <sup>62</sup>	Consensus report	Periodontitis is a chronic multifactorial inflammatory disease associated with dysbiotic plaque biofilms and characterized by progressive destruction of the tooth-supporting apparatus. Its primary features include the loss of periodontal tissue support, manifested through clinical attachment loss and radiographically assessed alveolar bone loss, presence of periodontal pocketing and gingival bleeding. Representing the forms of destructive periodontal disease that are generally characterized by slow progression.

**Chart 1.** Main periodontal diseases, author / year, kind of study, definition (conclusion)

Main Periodontal Diseases	Author / Year	Kind of study	Definition
Aggressive periodontitis	Papapanou et al., 2018 <sup>62</sup>	Consensus report	A diverse group of highly destructive forms of periodontitis affecting primarily young individuals, including conditions formerly classified as “early-onset periodontitis” and “rapidly progressing periodontitis”, where it is possible to identify a powerful bone destruction and fast clinical attachment loss, as the main clinical manifestations, even if the amount of plaque accumulated is not consistent with such results. It can be generalized, when it affects several teeth or localized, that usually occurs in incisors and first molars.
Periodontitis as a manifestation of systemic disease	Papapanou et al., 2018 <sup>62</sup>	Consensus report	It is a heterogeneous group of systemic pathological conditions that include periodontitis as a manifestation. Systemic etiologic components may be present in patients who exhibit periodontal inflammation or destruction disproportionate to local irritants. In these cases, in addition to a complete periodontal examination, laboratory tests and consultations with other health professionals may be requested.
Necrotizing periodontal diseases	Herrera et al., 2018 <sup>60</sup> Papapanou et al., 2018 <sup>62</sup> ; Caton et al., 2018 <sup>63</sup>	Consensus report	In this single division, periodontitis show a group of conditions that share a characteristic phenotype where necrosis of the gingival or periodontal tissues is a prominent features. They are a low disease, their importance is clear, because they represent the most severe conditions associated with dental biofilm, leading to very rapid tissue destruction.
Periodontal abscesses	Herrera et al., 2018 <sup>60</sup> Papapanou et al., 2018 <sup>62</sup> ; Caton et al., 2018 <sup>63</sup>	Consensus report	It is a clinical entity with distinct diagnostic features and treatment requirements, formed by an accumulation of pus located in the periodontium, they are the result of an acute or chronic inflammation. can specifically be defined as a localized accumulation of pus located within the gingival wall of the periodontal pocket, with an expressed periodontal breakdown occurring during a limited period of time, and with easily detectable clinical symptoms.
Endodontic-periodontal lesion	Herrera et al., 2018 <sup>60</sup> Caton et al., 2018 <sup>63</sup>	Consensus report	Differentiating the periodontal lesions of endodontics is not very complicated, because it is clear in clinical and radiographic signs that the lesion is close to the apex of the teeth in cases of endodontics; in the case of periodontal lesions, they are found in the regions near the marginal periodontium. The possibility of this interrelation must be demonstrated through a complete diagnosis, with the patient's history, results of clinical exams and radiographs. In spite of being relatively rare in clinical practice, might severely compromise the prognosis of the tooth, and are considered one of the most challenging problem faced by clinicians because they require multidisciplinary evaluation, diagnosis, and treatment.

## Interrelation between Diabetes and Periodontal Disease

In cases where there is an association of two or more diseases, improving the individual's well-being and life quality becomes more complex, especially when these diseases have a bidirectional relation, as observed between diabetes mellitus and periodontal disease<sup>28</sup>.

For more than thirty years, the association between diabetes mellitus and periodontal disease has been investigated and, today, there is a lot of scientific evidence to prove this relation hypothesis. Both present high rates of prevalence in the general population (1% to 6% of diabetes and 14% of periodontitis), have several causative factors and have chronicity characteristics<sup>29</sup>. Patients with diabetes mellitus may present with oral manifestations such as: halitosis, xerostomia, ulcerations, burning mouth syndrome (glossodynia), fungal infections, palate changes, fissured tongue, cheilitis, lichen planus, enamel hypocalcification, periodontal disease, dental caries and difficulty in the retention of removable dentures<sup>30</sup>.

The dental surgeon must have a preparation to guide and promote the dental treatment of his patients with diabetes. Being aware or not of such condition, it is the professional's role to perform examinations and make a careful analysis, to obtain knowledge of the patient's systemic condition and to control of possible diseases<sup>31</sup>. Patients with diabetes should have a medical follow-up. However, it is up to the periodontics to be aware of the presence or recurrence of abscesses, gingival hyperplasia, rapid destruction of the alveolar bone and difficulty of healing after surgery or periodontal procedures, because these alterations may indicate that the glycemic control is occurring inadequately<sup>32</sup>.

Some studies affirm that there is no relation between these diseases; however, current epidemiological methods show that diabetes is not only one of the risk agents for the establishment of periodontal disease. Indeed DM is capable of altering the condition or even exacerbating preexisting periodontal disease in the diabetic individual, acting as a modifying factor of periodontal disease<sup>33-36</sup>. In diabetics, periodontal diseases exert action on the liver, acting on proteins, stimulating their release, still alter lipid metabolism

and have effects on beta cells of the pancreas<sup>37</sup>. Patients with DM tend to have a decrease in salivary flow, which contributes to the greater susceptibility of trauma damages or the appearance of infections; this is because hyposalivation or even xerostomia contributes to a greater accumulation of bacterial biofilm, which is one of the primary factors for the appearance of periodontal diseases<sup>38</sup>.

Studies have reported that diabetes is considered a risk factor for gingivitis and periodontitis; in addition, periodontitis may also contribute to difficult glycemic control in diabetic patients, increasing the risk of clinical complications associated with diabetes, by activating immunoinflammatory response of the host<sup>39-41</sup>. Periodontal diseases are involved in the activation of the host immune system by producing proinflammatory cytokines of monocytes and polymorphonuclear leukocytes including interleukins (IL) - 1 $\beta$ , IL-6, IL-8, tumor necrosis factor alpha (TNF- $\alpha$ ) and prostaglandin E<sub>2</sub><sup>42</sup>. Increased production of cytokines provides an exaggerated immune response, leading to the destruction of periodontal tissues and, when present, biofilm consists predominantly of Gram-negative bacteria such as *Porphyromonas gingivalis*, *Tannerella forsythia* and *Prevotella intermedia*, which lead to increased levels of C-reactive protein and fibrinogen<sup>43</sup>. These cytokines can reach the systemic circulation and lead to an elevated inflammatory state which, in the case of diabetic patients, will lead to an increase in insulin and glucose resistance<sup>44</sup>.

Tunes et al. (2010) proposed a mechanism that justifies the relation between periodontitis and the development of insulin resistance in patients with type II diabetes mellitus<sup>45</sup>. Therefore, inflammatory mediators triggered by the presence of periodontitis may interact with lipids, free fatty acids and end products<sup>46</sup>. This interaction induces the activation of intracellular pathways such as IK $\beta$  (I-kappa-B), IKK $\beta$  (I-kappa-B kinase- $\beta$ ), NF- $\kappa$ B (nuclear kappa factor), JNK (N-terminal kinase protein C), all of them strongly associated with insulin resistance<sup>47</sup>. The activation of all these inflammatory pathways in cells of the immune system (monocytes and macrophages), endothelial cells, adipocytes, hepatocytes and muscle cells contribute to and increase insulin resistance, making metabolic control difficult in patients with both pathologies<sup>48</sup>.

With the release of cytokines and other mediators of inflammation (C-reactive protein, plasminogen activator/inhibitor-1, tumor necrosis factor alpha and interleukin-6), recruitment of monocytes into connective tissue occurs<sup>49</sup>. Thus, the cellular differentiation of monocytes into macrophages occurs, accompanied by the release of inflammatory mediators, causing the inflammatory response to spread to various tissues and organs, particularly insulin susceptible ones, such as liver and skeletal muscle<sup>50-53</sup>. On the other hand, cytokines, bacterial lipopolysaccharides, lipids, free fatty acids and other products of bacterial metabolism lead to the activation of the intracellular I-kappa- $\beta$  (IK $\beta$ ) pathways; IKK $\beta$  (I-kappa- $\beta$  kinase- $\beta$ ), NF-k $\beta$  (nuclear kappa factor), JNK (N-terminal Kinase of protein C)<sup>54-57</sup>. JNK promotes insulin resistance through the phosphorylation of serine residues in the insulin receptor (substrate 1)<sup>46</sup>. Activation of IKK $\beta$  leads to the phosphorylation of IK $\beta$  (cytosolic NF-k $\beta$  inhibitor). NF-k $\beta$  is a protein transcription factor involved in the transcription of several genes, directly related to insulin resistance (TNF- $\alpha$ , IL-1, IL-6 and IL-8)<sup>58</sup>.

Once the immune-inflammatory response is activated, it can be maintained through the constant positive response of pro-inflammatory cytokines<sup>59</sup>. Periodontitis may also lead to the migration of Gram negative bacterial species present in the periodontal biofilm into the systemic circulation leading to bacteremia<sup>60</sup>. In view of the seriousness of this clinical picture, it is important to have adequate therapy, as well as routine visits to the doctor and dentist in a way that prevents the progression of diabetes mellitus or periodontitis<sup>61-64</sup>.

### Final considerations

#### It can be concluded from this study that:

Diabetes mellitus and periodontal disease are diseases of high prevalence in the population and present a bidirectional interrelation, both of which influence their respective mechanisms and can improve or worsen the situation of their cases. Due to the exposed in the literature on the interrelation of diabetes mellitus and periodontal disease, further studies are needed for a better understanding of the

subject, knowing that the interdisciplinary approach is very important for the patient to have a better quality of life.

### Authors Contributions

Lopes GRS participated in the concepts and ideas stage for the research in question, project preparation, definition of the intellectual subject, bibliographic search, data tabulation, data analysis, preparation, revision and editing of the manuscript. Pinto AD participated in the concepts and ideas stage for the research in question, project preparation, definition of the intellectual subject, bibliographic search, data tabulation, data analysis, preparation, revision and editing of the manuscript. Lage KS participated in the bibliographic search phase in the databases of bibliographic cataloging. Diamantino PJS participated in the translation, revision and editing of the manuscript. Matos JDM participated in the stage of concepts and ideas for a research in question, confection of the project, revision of the intellectual subject, preparation, revision and editing of the manuscript. Andrade VC participated in the concepts and ideas stage for the research in question, project preparation, definition of the intellectual subject, bibliographic search, data tabulation, data analysis, preparation, revision and editing of the manuscript.

### Competing interests

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