BIOCHEMICAL AND IMMUNOLOGICAL INTERACTION BETWEEN DIABETES MELLITUS AND PERIODONTAL DISEASES IN ORTHODONTICS

INTERAÇÃO BIOQUÍMICA E IMUNOLÓGICA ENTRE A DIABETES MELLITUS E DOENÇAS PERIONDONTAIS NA ORTODONTIA

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Uniterms:

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ABSTRACT

Periodontal disease is complex once it involves disorders that affect the tissues. The main etiologic agent of the periodontium disease is the bacterial plaque and in its most advanced stages there might be loss of the teeth adhesion to the periodontal and the gingiva, with consequent local bone resorption, resulting in tooth loss. Diabetes mellitus is one of the most common chronic diseases in most countries and it is increasing in number and relevance. In 2019 was estimated that 463 million adults suffered from diabetes mellitus, a metabolic disorder known as being associated to various systemic diseases, as well as being associated with many problems in the oral areas. Studies have shown that diabetes, if untreated, can lead to the development of periodontal diseases. Several mechanisms have been suggested to explain the increased susceptibility to periodontal diseases, including changes in host response, subgingival microflora, gingival crevicular fluid and inheritance patterns. Multiple pathophysiological mechanisms are also associated with increased alveolar bone loss found in diabetic patients. The bidirectional inter-relationship between diabetes mellitus and periodontal diseases typifies a classic example of how a systemic disease can predispose to an oral infection and of how it can exacerbate a systemic condition.

Unitermos:

Doenças periodontais;
Diabetes mellitus;
Ortodontia

RESUMO

A doença periodontal é complexa, pois envolve distúrbios que afetam os tecidos. O principal agente etiológico da doença periodontal é a placa bacteriana e em seus estágios mais avançados pode haver perda da adesão dos dentes ao periodonto e gengiva, com consequente reabsorção óssea local, resultando em perda dentária. O diabetes mellitus é uma das doenças crônicas mais comuns na maioria dos países e está aumentando em número e relevância. Em 2019 foi estimado que 463 milhões de adultos sofreu com a diabetes mellitus, um distúrbio metabólico conhecido por estar associado a várias doenças sistêmicas, além de estar associado a diversos problemas nas áreas bucais. Estudos têm demonstrado que o diabetes, se não for tratado, pode levar ao desenvolvimento de doenças periodontais. Vários mecanismos têm sido sugeridos para explicar o aumento da suscetibilidade às doenças periodontais, incluindo mudanças na resposta do hospedeiro, microflora subgengival, fluido gengival e padrões de herança. Múltiplos mecanismos fisiopatológicos também estão associados à perda óssea alveolar aumentada encontrada em pacientes diabéticos. A inter-relação bidirecional entre diabetes mellitus e doenças periodontais tipifica um exemplo clássico de como uma doença sistêmica pode predispor a uma infecção oral e como pode exacerbar uma condição sistêmica

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INTRODUCTION

Despite advances in the oral health of the population in several countries, global problems still persist and occur mainly among the less privileged groups in both developed and developing countries. Oral diseases, such as dental caries, periodontal diseases (PD), tooth loss, oral mucosa lesions, oropharyngeal cancer and oral diseases related to acquired human immunodeficiency syndrome (AIDS) are one of the main public health problems worldwide. Impaired oral health can cause adverse health effects in general and several oral diseases are associated with chronic diseases, for example, diabetes mellitus (DM)[1].

The DM is a chronic disease characterized by hyperglycemia resulting from defects in insulin action or secretion, and while type 1 DM is caused by failure in insulin secretion due to autoimmune damage of beta cells of the pancreas, type 2 DM occurs when the body is nonresponsive to insulin, and is associated with overweight/obesity and elevated hepatic glucose levels. It is a multifactorial disease that affects more than 463 million people worldwide, being one of the 10 most common causes of death in developed countries[2-4].

When uncontrolled, DM is associated with increased susceptibility to oral infections, including periodontitis[5,6], since PD is more frequent and severe in diabetic individuals who have advanced systemic complications, and this evidence affirms the relationship between DM and PD, especially in hyperglycemic patients[7-9].

Several factors associated with DM can influence the progression and aggressiveness of PD, such as the type of DM, patient age, disease duration and inadequate metabolic control[10]. Knowing that the periodontal microbiota in patients with DM is similar to that of non-diabetics, other factors, such as hyperglycemia and abnormalities of the immune response against oral infections seem to be responsible for the higher prevalence of these complications in diabetic individuals[11,12].

DM causes endocrine-metabolic abnormalities that alter homeostasis. Insulin deficiency, absolute or relative, stands out within endocrine abnormalities, and within metabolic abnormalities important disorders of carbohydrate, lipid and protein metabolism are involved. The most common symptoms are polyuria, polydipsia and polyphagia, greater susceptibility to infections, retinopathies, nephropathies, cardiovascular diseases, neuropathies, osteopenia and PD[13,14].

In addition, other manifestations can be found, for example, decreased polymorphonuclear cells and leukocyte function, abnormal collagen metabolism and longer time in the wound healing process and changes in protein metabolism, which may be responsible for the greater difficulty in responses measures in diabetic patients[15].

Bone is a dynamic tissue that undergoes changes even after the end of skeletal growth, comprising the remodeling process, a balance between apposition and bone resorption. Orthodontic movement involves a series of biochemical changes that culminate in bone tissue reabsorption on the pressure side and apposition on the tension side, that is, orthodontic forces trigger a remodeling process promoting tooth movement[16].

Glycemic control and monitoring of DM are important to reduce the impact of acute oral infections and microvascular complications and, in the case of diabetic patients who are under medical control, all dental and orthodontic procedures can be performed[12,17].

Future research is necessary to elucidate some questions regarding the relationship between PD and DM, the evidence available in the literature highlights a strong interaction between these two diseases and, also, the importance of adopting appropriate therapeutic approaches that include a medical approach. Therefore, the aim of this literature review is concerning the influence of DM and periodontal disease during application of orthodontic forces.

Periodontal disease

In healthy individuals there is maintenance of a balance between the microorganisms present in the biofilm, found in the plaque and the host's immune response, occurring a specific defense that prevents the development of PD[18].

Studies indicate some microorganisms as etiological agents of periodontal disease, such as *Porphyromonas gingivalis, Bacteroides forsythus, Treponema denticola, Prevotella*

intermedia, Fusobacterium nucleatum, Eubacterium and *Spirochetes* in cases of chronic periodontitis, and *Actinobacillus actinomycetemcomitans, Campylobacter rectus* and *Eikenella corrodens* in aggressive periodontitis located. These microorganisms have virulence factors that increase their infectivity and provide the ability to multiply and persist in the periodontium[19].

In the more advanced stages of the disease, loss of tooth adhesion with periodontium and gum may occur, with consequent local bone resorption resulting in tooth loss[20].

The periodontium is the name given to all tissues involved in fixing the tooth to the bone, maxilla or mandible, it is a dynamic structure composed of tissues that support and surround the tooth, including the gingiva, the periodontal ligament, the cementum and the alveolar bone[21].

PD is a disease that affects tissues being divided into two groups: gingivitis and periodontitis. Gingivitis begins with the presence of gingival inflammation, limited to the protective tissues, induced by the bacterial plaque, without loss of the insertion of the connective tissue[22]. While the etiology of periodontitis is mainly bacterial, the pathogenesis of the disease being mediated by the host response, resulting from the interaction between environment, genetic and acquired risk factors[23].

The pathogenesis of PD is complex because it reflects a combination of the onset and maintenance of the chronic inflammatory process, characterized by the diversity of microflora and its numerous bacterial products. In addition, the host's response against this infection is mediated by a complex pathway involving tissue destruction. Additional factors contribute to this process in the oral cavity including systemic diseases, especially DM, which can amplify the host's response against local microflora resulting in periodontal destruction[24].

Periondotitis is characterized by the presence of gingival inflammation with loss of insertion of connective tissue and resorption of the coronal portion of the tooth. Both diseases require the presence of plaque that induce pathological changes in tissues directly or indirectly[25].

The main etiological agent of periodontal disease is bacterial plaque, consisting of gram-negative anaerobic microorganisms whose accumulation induces an inflammatory response and leukocyte infiltrate[26].

Diabetes mellitus

The DM is metabolic disorder associated with systemic diseases, such as cardiovascular disease, kidney failure, neuropathy, retinopathy, visual impairment, blindness and periodontal disease[14]. In 2019, it was estimated that there are approximately 463 million diabetic individuals worldwide, and the number is expected to rise to 700 million by 2045, due to population expansion, increased ageing, reduced physical activity and dietary changes[4].

In Brazil, it was estimated that such a disease affected around 16.8 million people in 2019[27] and, although developed countries have a higher prevalence of the disease, the incidence tends to be higher in developing countries, as the aging population and changes in nutritional patterns lead to an increase in the prevalence of overweight/obesity[28].

Type 1 DM is the most common endocrine-metabolic disorder among children and adolescents and has a higher incidence in individuals between 10-14 years old. The cause is an absolute deficiency in insulin secretion, as the beta cells of the pancreatic islets are destroyed (autoimmune processes mediated by T lymphocytes), which makes the patient totally dependent on exogenous insulin[29]. On the other hand, type 2 DM (most prevalent) occurs due to a combination of resistance to insulin action and an inadequate compensatory insulin secretion response. In this type diabetes mellitus, hyperglycemia develops progressively and usually begins after 40 years old[30].

Patients with type 1 DM are those who are more susceptible to microvascular changes[31] and studies related to tooth movement and DM show that the disease promotes delayed bone regeneration, weakened periodontal ligament[32], microangiopathies in the gingival area[16,32] and larger and more severe gaps in the walls of the alveolar bone[16]. The capacity for new bone formation is reduced due to the apoptosis of fibroblastic and osteoblastic cells in diabetic individuals[33].

The healthy lifestyle of individuals causes a delay in the onset of the first symptoms of type 2 DM and reduces its incidence by 40-60% in high-risk individuals[34]. A study carried out with 3.234 non-diabetic people with the presence of risk factors, such as overweight or a sedentary lifestyle, showed a 58% reduction in the incidence of type 2 DM when a lifestyle intervention program was followed[35]. Furthermore, greater adherence to an overall healthy lifestyle is associated with a substantially lower risk of incidence and mortality cardiovascular disease among adults with type 2 DM[36].

Several pathogenic factors may be involved in the development of DM, such as genetic alterations, primary destruction of pancreatic beta cells due to inflammation, cancer, surgery

or trauma, endocrine complications such as hyperfunction of the anterior pituitary gland, Cushing's disease, pheochromocytoma and iatrogeny after administration of corticosteroids[29].

DM predisposes to the development of PD, and several mechanisms have already been identified (production of advanced glycosylation products, deficient immune response, inheritance of certain genetic polymorphisms, changes in blood vessels, connective tissue and salivary composition) and are involved in the pathophysiology of DM associated with PD. In the initial phase, gingivitis and periodontitis predominate and, if not detected early, these problems can progress to advanced PD[37].

In general, one of the characteristics of DM is the presence of an exaggerated inflammatory response that induces several systemic diseases to manifest, including in the oral cavity, such as periodontitis. Therefore, if the patient does not know about the existence of DM or if the professional does not recognize the signs of it in the oral cavity, the treatment can become complicated[38].

Correlation between periodontal diseases and diabetes mellitus

According to a longitudinal control case study, 82% of diabetic patients with severe periodontitis had cardiovascular, cerebrovascular problems and peripheral vascular events when compared to 21% of diabetic individuals who did not have periodontitis[39].

Several mechanisms have been proposed to explain the increase in susceptibility to PD, including changes in host response, subgingival microflora, collagen metabolism, vascularity, gingival crevicular fluid and hereditary patterns. Multiple pathophysiological mechanisms (impaired neutrophil function, decreased phagocytosis and leukotaxis) are also being linked to the increased loss of alveolar bone found in diabetic patients[40].

However, evidence suggests that bacteremia induced by periodontitis can cause increased levels of serum proinflammatory cytokines, leading to hyperlipidemia and, finally, causing an insulin resistance syndrome and contributing to the destruction of pancreatic beta cells, treatment of chronic periodontal infections is essential for the control of DM[41].

PD is characterized as a chronic disease with a higher incidence in human dentition and is correlated with DM, because when DM is not treated, it favors the development of PD, which is the sixth classic complication of DM[42]. Therefore, PD has a significant impact on the metabolic status of diabetics and the presence of periodontitis increases the risk of worsening glycemic control over time[43].

Immunological and biochemical correlation between periodontal diseases and diabetes mellitus

In hyperglycemic individuals, proteins become irreversibly glycated forming end glycosylation products (AGEs), and this link has several effects on cell-cell and cell-matrix interaction and believes that this is the main link between the various complications of DM, for example, increased vascular permeability and thrombus formation[44].

The function of neutrophils is often decreased in diabetics, monocytes and macrophages exhibit hyperregulation in response to bacterial antigens, this is due to a significant increase in the production of inflammatory cytokines and mediators[45].

The level of glycemic control in diabetic patients is related to the presence and severity of PD since these patients are at greater risk of developing periodontitis when compared to controlled and non-diabetic patients[46].

The signs of systemic inflammation are elevated in both types of DM. Systemic levels of tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) are elevated in diabetic individuals and can promote insulin resistance, therefore, high levels of these cytokines can be indicators of DM, and can play a causal role in the etiology of type 2 DM, and the tendency of diabetic individuals to have high levels of inflammation has serious consequences[47].

Some salivary components and decreased salivary flow may be involved in the characterization of the oral health of diabetic children, for example, acid pH decreases the salivary flow, excess foam is usually found in the saliva of diabetic children, the total of sugars, glucose, urea and proteins are higher in diabetic patients, that is, oral diseases can be caused by several factors, with microorganisms being one of the main factors. Thus, DM causes changes in the salivary glands, which contributes to an increase in the number of pathogenic bacteria, in addition, the low salivary flow can affect the oral flora by altering the composition of saliva, in addition to other determinants such as immunoglobulins A and G, calcium and potassium that are found at increased levels in the saliva of diabetic patients[48].

Diabetic individuals have changes in immune cell functions such as neutrophils, monocytes and macrophages, and neutrophil adherence, chemotaxis and phagocytosis are

impaired, which can inhibit bacterial death in the periodontium and significantly increase periodontal destruction[49].

The activation of death domain receptors, such as TNF receptor-1 (TNFR1) activated by cytokines or fas receptors (member of the TNF receptor family) is a mechanism that can lead to apoptosis processes of matrix-producing cells in individuals diabetics[50].

Interleukin-1 (IL-1) and gamma-interferon (IFN-γ) can promote apoptosis even in the absence of their death domain receptors, altering the expression of pro-apoptotic genes or by an increase in the production of radical oxygen species (ROS) and AGEs can promote apoptosis through caspase activity, as well as by an indirect pathway that increases oxidative stress, or by the expression of pro-apoptotic genes[51].

Monocytes, macrophages, neurons, endothelial cells and smooth muscle cells have on their surfaces a receptor that is activated by AGEs, called RAGE, and diabetic individuals have high levels of accumulation of periodontal AGEs when compared with non-diabetic individuals[52].

RAGE is activated by AGEs, and this interaction initiates an intracellular signaling determining a change in the cell phenotype. This modification generates a pro-inflammatory environment resulting in vascular changes and response to abnormal tissue repair. When macrophages expressing RAGE is activated, it determines the release of pro-inflammatory mediators such as IL-1, IL-6, IFN-y, TNF-α, increases oxidative stress and activates the transcription factor, the nuclear factor Kappa B (NF-κB), which activate osteoclasts and release metalloproteinases (MMPs) and, consequently, destruction of connective tissue and bone resorption occurs[46].

Studies show that the RAGE-AGEs interaction in the periodontal tissue of diabetic individuals increases the levels of IL-1, TNF-α and prostaglandin E2 (PGE2) when compared with non-diabetic individuals, thus, these pro-inflammatory cytokines contribute to the pathogenesis of PD, playing a greater role in diabetic patients, especially when there is no glycemic control[46].

The formation of ROS, TNF-α and AGEs can affect oral healing or the response to bacterial-induced periodontitis from a direct effect on fibroblastic or osteoblastic cells, leading to reduced collagen expression, or indirectly, promoting inflammation and apoptosis of the matrix-producing cells, thus, diabetic individuals, who have increased levels of ROS, TNF and AGEs have impaired healing response or even PD progression[33] (Figure 1).

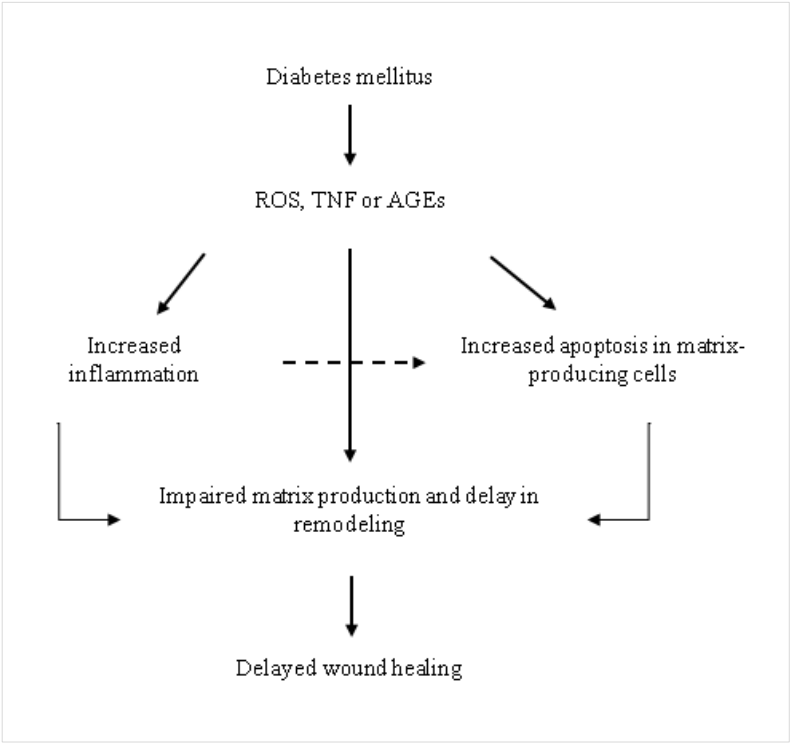

Figure 1: Probable mechanisms that diabetes mellitus can affect wound healing. The production of ROS, TNF or AGEs induced by diabetes mellitus can have a direct effect on the repair, which includes the inhibition of collagen production by osteoblasts, fibroblasts derived from the gums or skin. However, they can have indirect effects on inflammation or increased apoptosis. Together, these direct and indirect effects of AGEs can contribute to wounds in diabetics. Adapted from Graves et al., 2006.

Periodontal ligament fibroblasts (FDLPs) and gingival fibroblasts (GF) are the main cells

of periodontal connective tissue and are activated when microorganisms invade the epithelial barrier. Its function is involved in the release of cytokines and degradation molecules, where GFs produce TNF-α, IL-6, IL-8, alpha-1 macrophage inflammatory protein (MIP) and stroma-derived factor (SDF-1) that they are important molecules in the regulation of inflammatory processes and bone metabolism. FDLPs are involved in the expression of the MMPs matrix, laminin 2/4 and laminin 8/9, however, these cells contribute to periodontal inflammation and bone loss through the production and release of IL-1, IL-6 and TNF-α[53].

The cells involved in the host's innate response include FDLPs, GF, epithelial cells and osteoblasts. Epithelial cells are involved in the production of IL-8 and neutrophils in the production of chemokines. In the periodontal region, neutrophils are the first cells to reach and increase their production of pro-inflammatory cytokines, IL-1, IL-6 and TNF-α, which induce the destruction of periodontal tissue by stimulating bone resorption. Monocytes can differentiate into osteoclasts (multinucleated giant cells), specialized in resorption and produce pro-inflammatory cytokines[54].

Orthodontics and diabetes mellitus

The bone resorption process occurs constantly, being carried out from small cell groups called basic multicellular units (BMU) composed of osteoclasts, osteoblasts and macrophages[55].

Uncontrolled or poorly controlled diabetic patients are at risk of accelerating the process of periodontal degradation, which contraindicates orthodontic treatment until the metabolic disorder is compensated. It is important to obtain a previous periodontal examination of the oral region, including evaluation of plaques and gingivitis and to verify the need for periodontal treatment, since the periodontium must be in favorable conditions, as well as the inflammation process must be controlled before the beginning of any orthodontic treatment. On the other hand, if diabetes is properly controlled, the bone and periodontal response to orthodontic forces is practically normal and can achieve a satisfactory orthodontic result[29].

The orthodontic movement is performed from the remodeling of the alveolar bone in response to a mechanical action and bone resorption is caused by the activity of osteoclasts on the compression side and by osteoblasts forming new bone on the tension side. Therefore, any change in metabolic status can interfere with bone remodeling resulting in a different rate of tooth movement[56].

Regarding orthodontic movements, cell migration induced by chemokines are involved in the remodeling of paradental tissue and the chemokines MCP-1/CCL2, MIP-2/CXCL2 and RANTES/CCL5 are quite expressed during orthodontic movements, especially in the orthodontic zone pressure[57].

Chemokines (MCP-1, MIP, SDF-1) are capable of inducing differentiation into osteoclasts, activating bone resorption and promoting their survival. However, although osteoclast differentiation can be done by the interaction of chemokine-chemokine receptors, their activation is dependent on the link between RANK-RANKL[58].

The response of patients to orthodontic forces has been described as a transient and aseptic inflammation mediated by a variety of endogenous mediators, such as cytokines and chemokines, which are recognized as being essential for the recruitment of osteoclast and osteoblast precursors, and also for bone cell development, activation and survival[59]. Such precursors express chemokine receptors, such as CCR2 and CCR5, therefore, chemotactic signals from chemokines (MCP-1/CCL2, MIP-1α/CCL3, SDF-1/CXCL12) are essential to direct migration to bone tissues[60].

Orthodontic treatment is based on the principle that prolonged applications of pressure on the tooth that will result in a movement that is a consequence of the remodeling of the surrounding bone so that the success of the treatment depends on the bone response to the applied forces, therefore, the healthy bone is fundamental for obtaining the planned dental movements[61].

Among the medical conditions frequently found in orthodontic patients is DM and, knowing that this disease results in bone remodeling, inducing a decrease in mineral density, osteopenia, osteoporosis and an increase in the prevalence and severity of PD, DM can affect orthodontic movement[62].

The need for orthodontic treatment in adult

and diabetic patients is often associated with occlusion problems related to periodontal degradation and tooth loss, whereas in young diabetic patients one of the reasons is the occurrence of abnormalities in oral development[61].

Patients with type 1 DM have lower values of mineral bone density. According to a study that analyzed the bone response of diabetic rats treated and not treated with insulin after application of orthodontic forces, it concluded that bone activity in the periodontal cortex of dental alveoli had a significant decrease in bone formation and erosive areas in diabetic rats when compared to controls, however, the recovery of these parameters was observed in diabetic rats when they were treated with insulin and submitted to experimental orthodontics (Figure 2). Therefore, the bone response to orthodontic forces in diabetic individuals treated with insulin does not differ significantly from that observed in healthy individuals[61].

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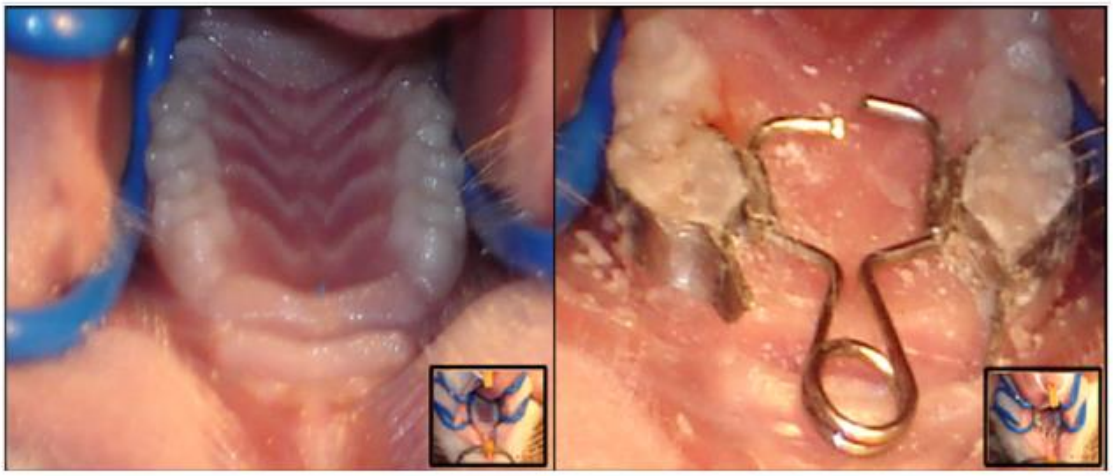

Figure 2: Photograph showing the orthodontic device, before and after being placed on the mouse. Adapted from Villarino et al, 2011.

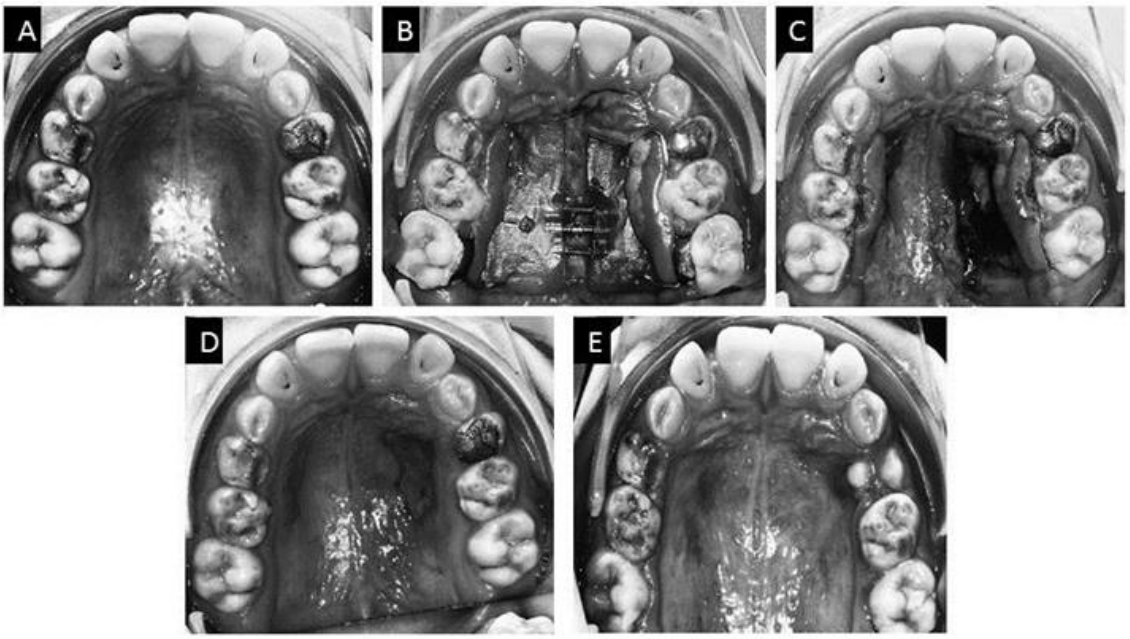

Figure 3: Image of the occlusion of a diabetic patient at nine years old undergoing orthodontic pretreatment with a maxillary expander (A), after one week of treatment (B), one week after treatment and removal of the maxillary expander (C), regression of the lesion 15 days after removal of the maxillary expander (D) and retention phase of the second attempt performed with the maxillary expander after controlling diabetes mellitus (E) with a normal aspect of orthodontic treatment. Adapted from Maia et al., 2011.

In a case report, a nine-year-old child had an unusual reaction to orthodontic treatment performed after the application of a maxillary expander. Follow-up examinations were carried out and the patient was found to have DM. After disease control, a new orthodontic treatment was proposed and there was no unusual reaction (Figure 3)[38].

Therefore, people with DM should not receive orthodontic treatment until the metabolic state is normalized and, once the disease is controlled, orthodontic treatment can be resumed. Thus, the presence of unusual responses to orthodontic treatments is a suspicion that there may be some systemic impairment in the patient, such as DM, so that the orthodontist plays an important role in identifying patients with such impairments.

DISCUSSION

Over the past decades, many studies have been developed in order to clarify the mechanisms that lead to the association between DM and PD.

Periodontitis is characterized by loss of conjunctive insertion, including destruction of the periodontal ligament and alveolar bone support, resulting in the formation of the periodontal pocket, occurring due to microbial accumulation modulated by a series of environmental, local and systemic factors[22] by example DM and smoking, called risk factors which modify the onset and progression of periodontal infection[63].

In a study whose objective was to assess the association between metabolic control and oral health in adolescents with type 1 DM, it showed that poor metabolic control was prevalent among adolescents with type 1 DM (76%) when compared to non-diabetic adolescents, the which demonstrates that the oral health of adolescents with type 1 DM is impaired regardless of metabolic control[64].

Another study comparing type 1 DM individuals with non-diabetic individuals, evaluated the frequency of PD in these groups and the relationship with DM metabolic control, duration and presence of complications, demonstrated that diabetic patients have higher bleeding rates, more periodontal pockets deep, and greater losses of periodontal insertion, that is, patients with type 1 DM have a tendency to have increased susceptibility to PD, particularly in those with deficient metabolic control or with complications from DM[65].

Periodontal health was examined and compared between 95 children with type 1 DM and 61 healthy individuals (4-14 years old) and the plaque index, gingival index, loss of insertion and bleeding were assessed. Diabetic children had high levels of plaques, gingival index and greater bleeding when compared to controls, which demonstrates that PD in young patients with type 1 DM is more evident than those non-diabetic patients[66].

Additionally, studies were carried out to demonstrate the association between type 2 DM and PD. It found that, in a total of 14.747 residents of a community (between 35-44 years old), the prevalence of PD was 10% higher in individuals with type 2 DM when compared to non-diabetics, therefore, type 2 DM was positively associated with the risk of developing PD[67].

In the United States of America, an investigative study was carried out to identify associations between glycemic control of type 2 DM and the severity of PD. Data were obtained from a total of 4.343 individuals between 45-90 years old. Fasting individuals who had plasma glucose above 126 mg/dL were considered diabetic; those with poor DM control had glycosylated hemoglobin levels greater than 9% and those with satisfactory DM control had glycosylated hemoglobin levels less than or equal to 9%. Thus, individuals with poor DM control had a significantly higher prevalence of severe periodontitis than non-diabetics. Among individuals with satisfactory DM control, there was a trend towards a higher prevalence of severe periodontitis. Thus, these results corroborate the existence of an association between poor type 2 DM control and the severity of periodontitis[68].

Individuals with type 2 DM were at increased risk of destructive periodontitis when insertion loss was used to measure the disease. This demonstrates that DM increases the risk of developing destructive PD about three times, therefore, DM increases the risk of developing PD and periodontitis can be considered a potential complication of DM[69].

It is currently known that the interaction between RANKL, RANK and osteoprotegerin

(OPG), is important in the coordination of osteoclastogenesis and, thus, alveolar bone resorption[58,70]. The identification and characterization of the OPG/RANKL/RANK system as the dominant and final mediator of osteoclastogenesis represents one of the main advances in the pathogenesis of PD[71,72].

DM can alter bone remodeling, with osteopenia and osteoporosis being some of the complications. In addition, DM increases the risk and severity of chronic inflammatory PD, in which bone resorption occurs. Evidence suggests that chronic inflammation may contribute to the development of DM and its complications, with hyperglycemia being the key point, which may contribute to the maintenance of inflammation by increasing pro-inflammatory cytokines, which are known to cause insulin resistance via mechanisms mediated by the toll like-4 receptor (TLR-4)[73].

Studies have been carried out to evaluate the effect of high glucose levels on the biomineralization process and inflammation markers in human osteoblast cell line from the evaluation of the quantity and quality of calcium crystals deposit and protein expression associated with the biomineralization process, RANKL, OPG, cytokines (IL-1, IL-6, IL-8, IL-10, MCP-1, TNF-α) and the TLR-2, TLR-3, TLR-4 and TLR-9 receptors. High glucose concentrations have been shown to alter the biomineralization process in osteoblastic cells and cause increased mineralization and expression of RANKL messenger RNA (mRNA), decreased OPG, increased mRNA expression for osteocalcin, bone sialoprotein and transcription factor Runx2 (essential gene for osteoblastic differentiation, which activates and/or represses other genes involved in the formation of bone tissue), poor mineral quality and increased mRNA expression for IL-1β, IL-6, IL-8, MCP-1 and IL-10. In addition, high glucose levels and hyperosmotic conditions caused overexpression of TLR-2, TLR-3, TLR-4 and TLR-9 receptors in osteoblastic cells, which suggests that these cells are susceptible to osmotic stress[73].

Immunohistochemical studies have shown that patients with DM for less than 10 years have intense inflammatory infiltrates of lymphocytes and diabetic patients with evolution, over 10 years, have inflammatory infiltrates of less intense lymphocytes. The inflammatory infiltrate in diabetic patients with PD is polymorphic, mostly with a diffuse pattern in the gingival chorion. The intensity of the lymphocyte infiltrate is greater in patients with chronic periodontitis and DM for less than 10 years and T lymphocytes are more numerous when compared to B lymphocytes and are present both intraepithelial and under the gingival epithelium in all patients, regardless of DM evolution time[74].

Assessement of plasma levels of C-reactive protein (CRP),IL-1, IL-6 and TNF-α in gingival crevicular fluid in two groups of individuals with periodontitis and diabetics (type 1 or 2) identified differences in inflammatory mechanisms between the two classes of DM associated with PD. In study they found that the levels of IL-1 and TNF-α in the gingival crevicular fluid of individuals with type 1 DM were higher than in individuals with type 2 DM. Additionally, there was a negative correlation between the duration of DM and IL-1, and between the duration of type 1 DM and TNF-α, showing that the levels of IL-1 and TNF-α in patients with periodontitis and type 1 DM are affected by the duration of the disease[75].

The effects of DM on orthodontic tooth movement in diabetic mice exhibited remarkable orthodontic tooth movement and a high number of osteoclasts when compared to mice with normal glycemic control. This is associated with increased expression of factors involved in osteoclast recruitment and activity (*Rankl, Ccl2, Ccl5* and *Tnfα*) in diabetic mice, on the other hand, there was a decrease in osteoblast markers (*Runx2, Ocn, Col1* and *Alp*). The reversal of the diabetic state by insulin treatment resulted in morphological changes similar to mice with normal glycemic control. These results suggest that the diabetic state regulates osteoclast migration and activity positively and negatively differentiates osteoblasts, resulting in greater orthodontic tooth movement[62].

DM is a complex disease characterized by several variables that can influence the development of complications, including periodontitis and orthodontic treatments. Although the exact mechanisms of action are not fully elucidated, deficient metabolic control, as well as the duration of the hyperglycemic state, are risk factors for periodontitis and changes in host functions.

FINAL CONSIDERATIONS

In summary, it is clear that DM and periodontitis are diseases of high prevalence in the world population and the interrelationship between them represents a classic example of how a systemic disease can predispose to an oral infection and how it can exacerbate a systemic condition. Thus, DM and periodontitis can be considered as bidirectional diseases (whose biological mechanism involves the synthesis and secretion of pro-inflammatory cytokines).

DM is a risk factor for periodontitis and plausible biological mechanisms, exemplifying this interrelation, have been demonstrated. The impact of PD on the glycemic control of DM and the mechanisms of this association has been suggested, but further studies are required to elucidate this issue.

When DM is well controlled, it is not a contraindication for orthodontic treatments, however, during treatment, it is necessary to pay special attention to periodontal problems and patients should be notified about the great propensity for gingival inflammation when fixed applications are made used and also the importance of maintaining good oral hygiene in order to prevent the progression of periodontal destruction.

Therefore, orthodontic treatments should be avoided in patients with uncontrolled or poorly controlled DM, however, patients with good metabolic control, in the absence of local factors such as stones, and with good oral hygiene have gingival status similar to healthy patients, therefore, and they can be orthodontically treated.

AUTHORS CONTRIBUTIONS

VFG, LBC and MCO conceived the idea, wrote and reviewed the manuscript. All authors have read and agreed to the published version of the manuscript.

ABBREVIATIOS

DM: Diabetes mellitus; PD: doença periodontal; TNF- α: fator de necrose tumoral-α; IL: interleucina; TNFR1: receptor-1 de TNF; IFN-y: interferon gamma; ROS: radicais de oxigênio; NF-kB: fator nuclear Kappa-B; MMPs: metaloproteínases; PGE2: prostaglandina E2; FDLPs: fibroblasto do ligamento periodontal; GF: fibroblasto gengival; MIP: proteína inflamatória de macrófagos alfa-1; SDF-1: fator derivado do estroma; OPG: osteoprotegerina; TLR: receptor *toll-like*; PCR: proteína C reativa.

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