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| REVIEW

Uncontrolled diabetes mellitus*: a current understanding of the mechanisms underlying the disease that affect orthodontic tooth movement*

Diabetes mellitus *descontrolada: uma compreensão atual dos mecanismos subjacentes a doença que afetam o movimento dentário ortodôntico*

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ABSTRACT

With improvements in dental aesthetic requirements an increasing number of adults are seeking orthodontic treatment that, along with current lifestyle and eating habits of the adult population, makes orthodontists more likely to encounter patients with metabolic disorders such as diabetes mellitus. Speculated that the diabetic patient during orthodontic treatment may not experience a physiological healing process as a healthy patient. Therefore, the objective of this work is to present a current and contextualized review of the mechanisms by which uncontrolled diabetes mellitus impacts on bone remodeling and orthodontic tooth movement during the application of orthodontic forces. The following databases were searched MEDLINE (via PubMed), Scopus, Web of Science, SciELO, LILACS and open grey with these MeSH "bone remodeling", "diabetes mellitus", "orthodontic" and "tooth movement". Five articles remained after search strategy and were analyzed. In sum, no clinical studies were found, the evidence was limited to animal studies (rats). The results suggest that there are differences in bone remodeling and tooth movement during the application of orthodontic forces in animals with diabetes mellitus when compared to healthy animals, especially when the disease is associated with periodontal disease. However, the results are still controversial and may be due to different study protocols.

Indexing terms: Bone remodeling. Diabetes mellitus. Tooth Movement Techniques.

RESUMO

Com melhorias nas exigências estéticas dentárias um número crescente de adultos está em busca de tratamento ortodôntico que, juntamente com estilo de vida atual e hábitos alimentares da população adulta, torna os ortodontistas mais propensos a encontrar

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pacientes com distúrbios metabólicos como a diabetes mellitus*. Especula-se que o paciente diabético durante o tratamento ortodôntico pode não experimentar um processo fisiológico de cura como um paciente saudável. Portanto, o objetivo deste trabalho é apresentar uma revisão atual e contextualizada dos mecanismos pelos quais a diabetes mellitus descontrolada impacta na remodelação óssea e no movimento dentário ortodôntico durante a aplicação de forças ortodônticas. Foram pesquisadas as seguintes bases de dados MEDLINE (via PubMed), Scopus, Web of Science, SciELO, LILACS e* open grey *com os termos MeSH: "remodelação óssea", "diabetes mellitus", "ortodontia" e "movimento dentário". Cinco artigos permaneceram após a estratégia de busca e foram analisados. Em suma, não foram encontrados estudos clínicos, as evidências foram limitadas a estudos em animais (ratos). Os resultados sugerem que existem diferenças na remodelação óssea e na movimentação dentária durante a aplicação de forças ortodônticas em animais com diabetes mellitus quando comparados a animais saudáveis, especialmente quando a doença está associada à doença periodontal. No entanto, os resultados ainda são controversos e podem ser devido a diferentes protocolos de estudo.*

Termo de indexação: *Remodelação óssea. Diabetes Mellitus. Técnicas de Movimentação Dentária.*

INTRODUCTION

Orthodontics involves the induction of tooth movement by removable and fixed appliances, with or without modification of craniofacial growth, in order to treat tooth and / or jaw misalignment [1]. With improvements in dental aesthetic requirements, an increasing number of adults are seeking orthodontic treatment that, along with current lifestyle and eating habits of the adult population, make orthodontists more likely to encounter patients with metabolic disorders such as diabetes mellitus (DM).

DM is a chronic disease caused by inherited and / or acquired deficiency in the production of insulin by the pancreas (type 1 DM) or by the body's inability to respond adequately to the action of insulin produced by the pancreas (type 2 DM) leading to high amounts of blood glucose. Type 2 DM is much more common and accounts for about 90% of all global DM cases. After the age of 50, middle-income countries have the highest proportion of deaths attributed to high blood glucose, for both men and women. Except in high-income countries, the proportion of deaths attributable to high blood glucose for both men and women are highest in the age group 60-69 years. Globally, high blood glucose causes about 7% of deaths among men aged 20–69 and 8% among women aged 20 - 69 [2].

Uncontrolled DM has important negative health consequences. Chronic hyperglycemia is associated, in the long term, with dysfunction and insufficiency of several organs: peripheral and autonomic neuropathy, cardiovascular diseases, retinopathy, nephropathy and bone fragility [2]. Regarding oral manifestations, individuals with DM present higher incidence of dental caries, oral infections, xerostomia, oral burning syndrome, bone erosions and periodontal disease [3]. In the diabetes-periodontitis direction, hyperglycaemia is associated with an increased risk and severity of periodontitis. Studies indicate that DM increases the risk of periodontal disease by as much as three times when compared in healthy patients [4]. As these two conditions, DM and periodontal disease, are highly prevalent in the adult population and many adults are currently seeking orthodontic treatment, these conditions are likely to be present during treatment.

Bone fragility is usually present in DM and is considered a pathological complication of this disease. In type 1 diabetes, hip fracture risk is four to six times higher compared with those without diabetes. For type 2 diabetes, the increased risk is more modest, estimated at 1.34 (95% CI 1.19, 1.51). In these individuals, the bone presents several structural characteristics predisposing to fractures, including greater cortical porosity, smaller cortical area and less resistance of the bone material [5]. These characteristics suggest that the biomechanical quality of the bone is affected in individuals with DM.

Bone quality is maintained by the constant remodeling process, which is based on bone resorption and bone formation. Orthodontic tooth movement (OTM) depends on balanced bone remodeling. The OTM comprises multiple biological processes characterized by consecutive reactions of the periodontal tissue in response to biomechanical forces. The application of forces leads to the creation of pressure and tension sides in the tissues of the periodontium around the tooth. Bone resorption on the pressure side (caused by osteoclast activity) and bone formation on the tension side (induced by osteoblasts) lead to bone remodeling, which in turn causes tooth movement [6]. Resorption and bone neoformation occur without major damage in healthy experimental animals undergoing adequate orthodontic forces. However, in animals with DM, it has already been demonstrated that bone formation is decreased [7].

In the 1980s, the classic study conducted by Holtgrave & Donath [8] associated for the first time experimental DM with orthodontic forces in a histological study involving the mesial movement of the first upper molar in rats. The authors observed, in DM rats submitted to an orthodontic stimulus, tapering and microangiopathy of the periodontal ligament in the gingiva and a delay in bone regeneration. The authors concluded that these specific changes in periodontium were more pronounced after OTM in the DM rat group. Since then, several studies have suggested that DM can compromise this process [9-12]. Thus, it is speculated that the diabetic patient with uncontrolled glycemia may not experience a physiological healing process as a healthy patient.

Considering the increasing demand for orthodontic treatment in adults and the greater likelihood of them presenting type 2 DM, it seems important to understand the various mechanisms and underlying processes by which uncontrolled DM can affect orthodontic treatment. Therefore, the objective of this work is to present a current and contextualized review of the mechanisms by which uncontrolled DM during the application of orthodontic forces impacts on bone remodeling and orthodontic tooth movement.

Information sources and search strategies

The following databases were searched: MEDLINE (via PubMed), Scopus, Web of Science, Scientific Electronic Library Online (SciELO), Latin American and Caribbean Health Science Literature (LILACS) and open grey. In addition, we examined the lists of references of relevant studies to identify potentially eligible articles. No restrictions regarding publication date, language or status applied. The search strategy was with the terms Medical Subject Headings (MeSH) "bone remodeling", "diabetes mellitus", "orthodontic" and "tooth movement". After the electronic search, no clinical studies were found on the implications of DM in bone remodeling and OTM, the evidence was limited to animal studies (rats). Within the objective of this review, five articles remained after the search strategy and were analyzed.

Found studies

In the study by Braga et al. [9] 35 g of force was used for 3 days. In DM rats, the authors observed accelerated OTM, increased numbers of osteoclasts, a significant increase in mRNA expression of proinflammatory cytokines and chemokines, and markers of osteoclast activity and recruitment, and a decrease in mRNA expression of osteoblastic markers.

In the study by Plut et al. [13] 0.25 newton of force was used for 42 days. To the authors' surprise, in DM rats, no significant differences were found in OTM. The authors expected an increase in tooth movement after the application of force because bone formation (surface of osteoblasts) and alveolar bone volume were decreased in these animals.

Arita et al. [14] used 10 g of force for 14 days leading to a reduced rate of OTM in DM rats. The authors refuted Braga et al. [9] who observed accelerated OTM in DM rats, saying that the force used by them from 35g for a first upper molar in rats could correspond to more than one kilogram for a first upper first molar in human. The study by Arita et al. [14] did not observe the effect of DM on bone cells or periodontal biomarkers. Thus, the exact reason for the decrease in OTM remains uncertain in this study.

Sun et al. [11] used a force of 0.25 newton for 14 days leading to an increase of OTM in DM rats associated with increased osteoclast number and activity and decreased osteoblast activity.

In the study by Ferreira et al. [12] 40 g strength was used for 7 days. Among DM and non-DM groups, although bone loss was higher in DM rats, no significant differences were found in OTM. However, between DM and DM with induced periodontal disease groups, greater bone loss and greater OTM were observed when the disease was present, suggesting that the presence of periodontal disease may have an impact on the amount of dental movement.

DISCUSSION

Some studies that investigated bone remodeling alone in an experimental animal model of DM, without associating it with the application of orthodontic forces, have already demonstrated decreased osteoblasts [15], decreased osteoblasts and increased osteoclasts [16] and, controversially, decreased osteoclasts [17].

In DM, the patient is exposed to a series of metabolic alterations caused by hyperglycemia that favor periodontal destruction and impair bone remodeling

alone [18]. One of the hypotheses raised is that the bone resorption and, consequently, the OTM would be altered because the bone turnover is reduced due to the action of Advanced Glycation Endproducts (AGEs) [19]. To help understand the mechanisms described below, a brief explanation of the production of AGEs in uncontrolled DM follows.

Intracellular hyperglycemia is the main initial event for the formation of intracellular and extracellular AGEs. AGEs are derived from the reaction between the carbonyl group of monosaccharides (glucose, fructose and ribose) with the amino group of the proteins, forming highly reactive molecules (glyoxal, methylglyoxal and 3-deoxyglucosone) capable of reacting with the proteins through various chemical modifications (glycation, glycosylation, oxidation, etc.) and form stable AGEs. The accumulation of stable AGEs in the proteins of the extracellular matrix (ECM) leads to the formation of bonds that permanently alter the functions of the metal matrix proteins (MMPs) such as collagen, elastin and other serum proteins. There is increased deposition of MMPs, with a sequence of events affecting the mechanical properties (elasticity, brittleness, stretching, tensile strength, etc.) of the tissue that ultimately leads to organic dysfunction. AGEs recognize the AGEs receptor (RAGE), which belongs to the family of immunoglobulins that express in a variety of tissues where AGEs accumulate. The AGE-RAGE interaction usually involves the production of reactive oxygen species, the production of inflammatory cytokines (such as tumor necrosis factor α-TNFα), and the activation of the nuclear transcription factor of pro-inflammatory kappa B (NF-κβ) [20-22].

Studies suggest that AGEs and exposure to the deleterious effects of proinflammatory cytokines increase apoptosis of osteoblasts and also inhibit the differentiation of osteoblast precursor mesenchymal stem cells [15,16,19]. Other diabetic complications, such as impairment of endothelium-dependent vasodilation, vascular calcification, and defective angiogenesis may affect the development of osteoblast progenitors of the haematopoietic niche and the delivery of osteoblasts and osteoclasts to the bone remodeling unit by capillaries present in the Harves channels [23].

In the study by Ferreira et al. [12] bone loss was even greater in the diabetic group with periodontitis. In contrast, in the study by Braga et al. [9] and Sun et al. [11] the accelerated OTM in DM rats occurred in conjunction with a higher number of osteoclasts and a decrease in osteoblastic markers. Villarino et al. [10] observed a decreased number of osteoclasts and osteoblasts in DM rats, but without changes in bone volume.

In general, it seems that during the OTM in the studies of Braga et al. [9] and Sun et al. [11] bone formation was delayed at the site of tension and failed to follow the extensive bone resorption at the pressure site, and the consequences were increased space in the periodontal ligament and increased tooth movement.

The periodontal ligament obtains its strength from type I collagen fibers (COL-I), while type III collagen (COL-III) creates more delicate fibrils responsible for tissue elasticity. COL-III accumulation is believed to be increased relative to COL-I in the early stages of collagen remodeling, especially under stress and gradually replaced by COL-I until a normal proportion of COL-III / COL-I is achieved [24,25].

Although Li et al. [26] did not evaluate OTM, they found in DM rats a greater number of osteoclasts associated with a progressive accumulation of COL-III, a COL-I delayed accumulation (on both sides of tension and pressure), increase in the ratio COL-III / COL-I and enhancement of the proteolytic enzyme MMP-1. Results corroborated in the study of Zhang et al. [27]. These results suggest that the periodontal ligament is more vulnerable in DM and requires more time to remodel since a higher proportion of COL-III / COL-I persisted.

It is known that hyperglycemia suppresses the differentiation of osteoclasts induced by RANKL (nuclear factor activating receptor κB ligand). The bone remodeling process is highly integrated and the RANK / RANKL / OPG (osteoprotegerin) system is important in determining the differentiation of osteoclasts. This system interact to regulate the bone remodeling process and therefore also play roles in orthodontic tooth movement. The binding of RANKL, which is expressed in osteoblast cells, to RANK, which is expressed in osteoclast precursor cells, results in the differentiation of these cells into mature osteoclasts. OPG, which competes with RANK for the binding of RANKL, inhibits the differentiation of osteoclasts [28].

In the study by Braga et al. [9], higher OTM in conjunction with a greater number of osteoclasts in DM rats, were associated with increased mRNA markers of osteoclast activity and recruitment (RANKL and colony stimulating factor 1 - CSF1). Plut et al. [13] observed reduction of bone volume in animals with DM after orthodontically induced

tooth movement without any alteration or decrease in osteoclastic activity. Although no significant difference was found in the surface of osteoclasts in DM rats, the lower surface of osteoblasts was accompanied by lower RANK and OPG mRNA expression and higher RANKL / OPG ratio.

Exacerbation of the pro-inflammatory framework may help to explain changes in bone resorption in DM animals. In the study by Braga et al. [9] increased OTM occurred in conjunction with a significant increase in mRNA expression of proinflammatory chemokines (CCL2, CCL5 and TNF-α) in periodontal tissues.

In the study by Ferreira et al. [12], greater bone loss and higher OTM was observed when periodontal disease was present. Nogueira et al. [29] demonstrated that the orthodontic force exerted on diseased periodontal tissues modulates the response to periodontal disease by increasing the expression of mediators of inflammation, thus increasing bone resorption. The presence of periodontal disease may exacerbate the pro-inflammatory process because it is a disease characterized by inflammation of the periodontal tissue induced by the bacterial biofilm, leading to subsequent alterations in the bone and connective tissue homeostasis, destruction of the periodontal ligament and tooth loss [4].

Hyperglycemia increases the formation of AGEs the periodontium and increases the expression of RAGE. The accumulation of AGE and the interaction of AGEs with RAGE may contribute to osteoclastogenesis through increased expression of the receptor activator of the RANKL and OPG negative regulation [18]. In addition, the formation of AGEs also increases oxidative stress in the periodontal tissue. Invasive bacteria trigger the release of inflammatory cytokines, leading to an increase in the number and activity of neutrophils, which release reactive oxygen species into periodontitis [30].

Therefore, orthodontic treatment in patients with DM, especially those with uncontrolled or poorly controlled disease, is often complicated by the presence of compromised periodontium.

It is worth mentioning that the regulation of blood glucose level reduced the abnormal responses to orthodontic force application. Both insulin and metformin administration reversed the adverse effects of diabetes on OTM [10, 11, 14]. These results suggest that if diabetic patients have glycemic control, OTM will be not impaired by DM.

FINAL CONSIDERATIONS

The results suggest that there are differences in bone remodeling and tooth movement during the application of orthodontic forces in animals with DM when compared to healthy animals, especially when DM is associated with periodontal disease. However, the results are still controversial and may be due to different study protocols (eg, application time and amount of orthodontic force applied). The authors cited in this review advise that diabetic patients, who are not on controlled glycemia, should not receive orthodontic treatment, since the application of orthodontic forces has been shown to cause undesirable effects. Therefore, they should be referred to the doctor and dietitian to regulate their blood glucose. More long-term and well-planned studies are needed to determine the factors that affect and the impact of DM on bone remodeling during orthodontic tooth movement.

Collaborators

DG SAMARTINI, conceptualization, formal analysis, investigation, methodology, writing-review & editing. MOM RODRIGUES and CS SANTOS, writing-review & editing

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