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SYSTEMATIC REVIEW

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Effect of bisphosphonate use on orthodontic tooth movement: a systematic review

Efeito do uso de bifosfonatos na movimentação dentária ortodôntica: uma revisão sistemática

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ABSTRACT

Background: As bisphosphonates have an action mode which interferes in the osteo-resorptive process, their use during dental treatment may occasionally have side effects, such as: inhibition of tooth movement, delayed bone healing, and osteonecrosis in the maxilla and mandible. **Objective**: The present study proposed a systematic review of the literature on the effect of systemic use of bisphosphonates on orthodontic tooth movement. **Methods:** This systematic review was developed based on PRISMA guidelines and the inclusion criteria were: written in English, approach the relationship between the use of bisphosphonates and orthodontic movement as the research objective and experimental study in rats. We excluded studies which did not evaluate orthodontic movement and those in which bisphosphonates were not the main analytical substance. The question raised was: "Does the systemic use of bisphosphonates interfere in orthodontic movement?" Classification of the risk of bias that studies was verified using the SYRCLE. **Results:** We initially identified 51 articles in the electronic search. This number was then reduced to 13 publications after the analysis of titles and abstracts. And 8 articles included for final analysis. **Conclusion:** Most studies of this systematic review point to the fact that the systemic use of bisphosphonates during orthodontic treatment seems to reduce the extent and speed of tooth movement, thus extending the treatment duration.

KEYWORDS

Bisphosphonates; Bone and bones; Rats; Systematic review; Tooth movement techniques.

RESUMO

Contexto: Como os bifosfonatos possuem um modo de ação que interfere no processo osteorreabsortivo, seu uso durante o tratamento odontológico pode ocasionalmente ter efeitos colaterais, tais como: inibição da movimentação dentária, retardo na consolidação óssea e osteonecrose na maxila e mandíbula. **Objetivo:** O presente estudo propôs uma revisão sistemática da literatura sobre o efeito do uso sistêmico de bifosfonatos na movimentação dentária ortodôntica. **Métodos:** Esta revisão sistemática foi desenvolvida com base nas diretrizes e recomendações PRISMA e incluiu: estudos escritos em inglês, que abordavam a relação entre o uso de bifosfonatos e a movimentação ortodôntica como objetivo da pesquisa e do tipo experimental em ratos. Foram excluídos estudos que não avaliaram a movimentação ortodôntica e aqueles em que o bifosfonato não era a principal substância analisada. A questão levantada foi: "O uso sistêmico de bifosfonatos interfere na movimentação ortodôntica?" A classificação do risco de viés dos estudos foi verificada usando o SYRCLE. **Resultados:** Identificamos inicialmente 51 artigos na busca eletrônica. Esse número foi então reduzido para 13 publicações após a análise dos títulos e resumos. E 8 artigos incluídos para análise final. **Conclusão:** A maioria dos estudos desta revisão sistemática aponta para o fato de que o uso sistêmico de bifosfonatos durante o tratamento ortodôntico parece reduzir a extensão e a velocidade da movimentação dentária, prolongando assim a duração do tratamento.

PALAVRAS-CHAVE

Bisfosfonatos; Osso; Ratos; Revisão sistemática; Técnicas de movimentação dentária.

INTRODUCTION

Bone remodeling is the basis of tooth movement, in which osteoclasts act to promote reabsorption of mature bone, while osteoblasts promote bone neoformation. This process is regulated by several local and systemic factors. Regarding systemic factors capable of interfering with the bone remodeling process, it is possible to include the age, nutrition and consumption of different types of drugs such as bisphosphonates, especially in view of the high impact it causes on bone and bone tissue and the increased frequency of use in recent years [1,2].

Bisphosphonates currently represent the therapy of choice for treating osteoporosis and are indicated for preventing and treating skeletal complications in cancer patients. Are a class of drugs highly effective in the treatment of various bone diseases, such as osteoporosis, Paget disease and bone metastasis [3,4]. Used for the treatment of several osseous disorders. The main subtypes of are alendronate, ibandronate, risedronate, pamidronate, clodronate, and zoledronic acid [5]. Studies have shown that these drugs may influence the amount of tooth movement and root resorption during orthodontic tooth movement [6-8].

Among the BPs, alendronate (AL) is one of the most commonly used drugs for the treatment of bone disorders. In adition, bone preservation and maintenance with the use of BPs, but it is also known that long-term therapy may impair bone strength, inadvertently altering bone turnover and eventually causing osteonecrosis of the jaw, micro damage and even pathologic fractures [3]. Clodronate inhibits bone resorption induced by orthodontic force [9,10]. Zoledronate provide maximal anchorage in extraction space closure [10]. Risedronate has a marked effect in reducing the prevalence of periapical lesions and based on the information compiled in rodents, it can be assumed that the rate of orthodontic tooth movement and tooth relapse movement may be affected by the administration of risedronate [5].

In addition to joining hydroxyapatite crystals in a mineralized bone matrix, making the bone more resistant to the catabolic action of osteoclasts, bisphosphonates inhibit the function of these cells, inducing their apoptosis and blocking reabsorption, and therefore bone remodeling [11].

As bisphosphonates have an action mode which interferes in the osteo-resorptive process, their use during dental treatment may occasionally have side effects, such as: inhibition of tooth movement, delayed bone healing, and osteonecrosis in the maxilla and mandible. Thus, authors have suggested that these drugs may alter bone physiology and potentially hinder orthodontic treatment[11].

Case reports involving patients undergoing bisphosphonate treatment have described a lower rate of tooth movement in these individuals than in those who did not use bisphosphonates along with orthodontic treatment impairment, thus justifying the need to investigate the extent of changes in bone metabolism caused by consuming this drug. In view of the above, the present study proposed a systematic review of the literature on the effect of systemic use of bisphosphonates on orthodontic tooth movement [12,13].

MATERIAL AND METHODS

This systematic review was developed based on PRISMA guidelines and recommendations 2020 [14] and included scientific articles published until september 2023. The question raised was: “Does the systemic use of bisphosphonates interfere in orthodontic movement?”

Bibliographic research strategy and initial selection of studies

An electronic search was conducted in the following databases: PubMed, Medline, Scopus, Cochrane Library and Clinical Trials.gov. The following search strategies were employed in these databases involving the descriptors: Biphosphonates AND Orthodontic movement, without restrictions with respect to the year of publication. The inclusion criteria considered for selecting the articles were: written in English, approach the relationship between the use of bisphosphonates and orthodontic movement as the research objective and experimental study in rats. We excluded studies which did not evaluate orthodontic movement and those in which bisphosphonates were not the main analytical substance.

Due to the previously established inclusion and exclusion criteria, two evaluators (G.R.GL and M.C.M) blindly performed the first selection stage of the articles based on the individual

analysis of titles and abstracts of all works found in the referenced databases. When there was inconsistency among reviewers regarding the inclusion of the scientific articles within the systematic review, a meeting was held for discussion and consensus. Then, the references of each selected article were manually searched in an attempt to obtain articles not found in the first stage of the bibliographic search.

Evaluation of the methodological quality of the initially included studies

The initially selected studies were read in full and those that met the inclusion criteria were qualitatively analyzed through two tools based on the study of Michelogiannakis et al. (2018) [15], using the SYRCLE (Systematic Review Center for Laboratory animal Experimentation) tool adapted to verify aspects of the risk of bias of the included studies, which plays an important role in in vivo experiments (Table I), and the ARRIVE tool (Animal Research Reporting in Vivo Experiment), following the guidelines of Kilkenny et al. (2010) [22] (Table II).

RESULTS

We initially identified 51 articles in the electronic search. This number was then reduced to 13 publications after the analysis of titles and abstracts. The full texts were analyzed according to the inclusion and exclusion criteria, resulting in 8 articles qualified for the final analysis, as summarized in Figure 1.

The methodological characteristics of the in vivo studies selected, such as: authorship, year of publication, type of animal, gender, age, sample size, study groups, dose, frequency and time of drug use, applied force during orthodontic movement, experimental unit, evaluated parameters and analysis types performed are described in Tables III, IV and V, while the main results and conclusions of these studies are in Table VI. The risk of bias classification (evaluated through the SYRCLE tool) and the scores obtained from the qualitative analysis of the experimental criteria (performed according to the ARRIVE tool) are described in Tables I and II, respectively.

DISCUSSION

Considering that orthodontic forces promote physical and biological events critical to bone renewal, including recruitment of inflammatory cells, formation of new vessels and tissue remodeling, it is possible that the systemic use of drugs inhibiting the osteo-reabsorption process, such as bisphosphonates concomitantly

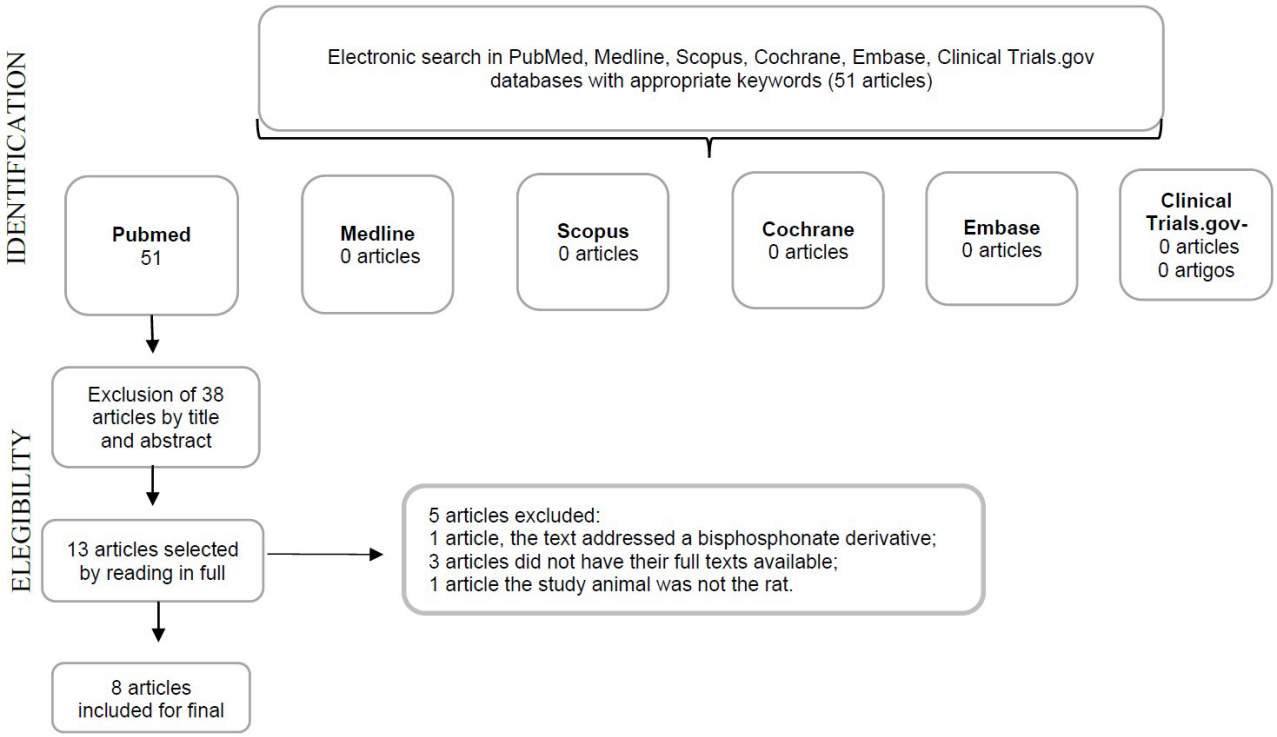

Figure 1 - Flowchart adapted from the PRISMA statement for systematic reviews [14].

Table I - Classification of the risk of bias verified using the SYRCLE tool, mean per item

N°	Risk of bias (SYRCLE)	Franzoni et al. (2017) [16]	Seifi et al. (2017) [17]	Brunet et al. (2016) [8]	Nakaš et al. (2017) [18]	Salazar et al. (2015) [7]	Kaipatur et al. (2013) [19]	Karras et al. (2009) [20]	Liu et al. (2004) [21]	Total (%)
1	Was the allocation sequence generated and applied properly?	NI	Yes	Yes	Yes	Yes	Yes	Yes	NI	Low bias (75%)
2	Were the groups similar at baseline or were they adjusted for confounding factors in the analysis?	NI	Yes	NI	NI	Yes	Yes	Yes	Yes	Low bias (62.5%)
3	Was the allocation sequence properly blinded?	NI	Yes	Yes	Yes	NI	Yes	Yes	Yes	Low bias (75%)
4	Were the animals randomly housed during the experiment?	NI	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low bias (87.5%)
5	Were caregivers and/or researchers blinded to the knowledge of intervention that each animal received during the experiment?	NI	NI	NI	NI	NI	NI	NI	NI	Inaccurate data (100%)
6	Were the animals randomly selected for outcome evaluation?	NI	NI	NI	NI	NI	NI	NI	NI	Inaccurate data (100%)
7	Was the outcome assessor blinded?	NI	Yes	NI	NI	NI	NI	NI	NI	Inaccurate data (87.5%)
8	Were incomplete data results adequately addressed?	NI	Yes	NI	NI	NI	NI	NI	NI	Inaccurate data (87.5%)

Legend: Low risk of bias: Proper randomization and concealment of allocation; answer "yes" to all questions about completeness of data and blindness results, and "no" in response to selective reporting and other sources of bias; Clear risk of bias: one or more criteria were partially met; or (iii) High risk of bias: one or more criteria were not met.

Table II - Scores of the experimental criteria analyzed qualitatively according to the *ARRIVE* tool

N°	ARRIVE Criteria	Franzoni et al. (2017) [16]	Seifi et al. (2017) [17]	Brunet et al. (2016) [8]	Nakaš et al. (2017) [18]	Salazar et al. (2015) [7]	Kaipatur et al. (2013) [19]	Karras et al. (2009) [20]	Liu et al. (2004) [21]	Total (%)
1	Title	1	1	1	1	1	1	1	1	100%
2	Abstract	1	1	1	1	1	1	1	1	100%
	Introduction									
3	General information	1	1	1	1	1	1	1	1	100%
4	Primary and secondary objectives	1	1	1	1	1	1	1	1	100%
	Metodology									
5	Ethical statement	1	1	1	1	1	1	1	1	100%
6	Study design, allocation concealment, blinding and randomization	0	1	1	1	1	1	1	1	87.5%
7	Experimental procedure with precise details	1	1	1	1	1	1	1	1	100%
8	Details of experimental animals, including species, sex, age, weight and source	1	1	1	1	1	1	1	1	100%
9	Housing and breeding conditions such as cage, light/dark cycle, temperature, access to food and water	1	1	1	1	1	1	1	1	100%
10	Sample size	1	1	1	1	1	1	1	1	100%
11	Allocation of animals to experimental groups, randomization	0	1	1	1	1	1	1	0	75%
12	Experimental results	1	1	1	1	1	1	1	1	100%
13	Statistical analysis	1	1	1	1	1	1	1	1	100%
	Results									
14	Baseline, animal health status	1	1	1	1	1	1	1	1	100%
15	Number of animals analyzed, reasons for exclusion	0	0	0	0	0	0	0	0	0
16	Results and estimation, results for each analysis	1	1	1	1	1	1	1	1	100%
17	Adverse events	0	0	0	0	0	0	0	0	0
	Discussion									
18	Interpretation, scientific implications, study limitations	1	1	1	1	1	1	1	1	100%
19	Generalization and translation, relevance to human biology	1	1	1	1	1	1	1	1	100%
20	Sources of financing, conflict of interest	1	1	1	1	1	1	1	1	100%
	Total score	16	18	18	18	16	18	18	17	19.37

Legend: Criteria classified as "0" (not reported) or "1" (reported).

Table III - Methodological characteristics of included studies

Author/year, country	Animal/Sex	Age	Sample size	Study groups
Franzoni et al., 2017 [16] (Brazil)	Male Wistar Rats	70 days	16	**Group 1:** Orthodontic movement and administration of alendronate sodium for 10 days; **Group 2:** Orthodontic movement and zoledronic acid for 10 days; **Control group:** Orthodontic movement and saline solution.
Seifi et al., 2017 [17] (Iran)	Male Wistar Rats	56 days	30	**Group 1:** Negative control (rats that did not receive orthodontic appliance); **Group 2:** Positive control group: rats receiving orthodontic appliances and 0.01 cc of 0.9% sodium chloride injectable solution; **Group ZA:** (Orthodontic appliance and 0.02 mg of ZA diluted in 0.9% sodium chloride injectable solution).
Nakaš et al., 2017 [18] (USA)	Male Wistar Rats	56 to 63 days	60	**Group E1:** application of 10 mMol clodronate; **Group E2:** application of 2.5 mMol of clodronate; **Group E3:** application of 10 mMol clodronate; **Group E4:** application of 2.5 mMol of clodronate.
Brunet et al., 2016 [8] (Brazil)	Male Wistar Rats	63 days	120	**Control group:** Orthodontic movement only; **Control group without movement:** animals that did not receive drugs or orthodontic movement; **Zoledronic acid control group:** animals receiving a single dose (0.1 mg/kg) of zoledronic acid without orthodontic movement; **Experimental group zoledronic acid:** animals given a single dose (0.1 mg/kg) of zoledronic acid.
Salazar et al., 2015 [7] (Brazil)	Female Wistar Rats	56 days	48	**OVX group:** ovariectomized rats; **Group OVX + ALN1;** Rats ovariectomized and treated with Sodium Alendronate at 1 mg/kg; **Group OVX + ALN2:** ovariectomized and treated with Sodium Alendronate at 2 mg/kg; **Control Group:** Rats with simulated operation.
Kaipatur et al., 2013 [19] (Canada)	Female Sprague Dawley Rats	48 days	20	**Group 1: (Control Group) -** 5 rats that received only saline solution; **Group 2: (bisphosphonate group) -** 0.015 mg of bisphosphonate and 8 weeks of orthodontic movement. **Group 3: (Saline group plus orthodontic movement) -** Saline solution and orthodontic movement for 8 weeks; **Group 4 (bisphosphonate group 2) -** 0.015 mg of bisphosphonate administered 12 weeks before and during the 8 weeks of orthodontic movement.
Karras et al., 2009 [20] (USA)	Male Sprague Dawley Rats	49 days	26	**Experimental group:** Rats were given 7 mg/kg body weight of Sodium Alendronate; **Control group:** Rats which did not receive treatment.
Liu et al., 2004 [21] (Japan)	Male Wistar Rats	63 days	120	**Control group:** Saline solution; **Experimental group:** 2.5, 10 and 40 mM Alendronate solution.

Table IV - Characteristics related to bisphosphonates and orthodontic tooth movement

Author/year, country	Bisphosphonate dosage and administration route	Time of bisphosphonate use	Force applied during orthodontic movement
Franzoni et al., 2017 [16] (Brazil)	2.5 mg/kg of subcutaneous sodium alendronate and 0.1 mg/kg of zoledronic acid	10 days	40c N
Seifi et al. 2017 [17] (Iran)	0.02 mg zolena Alendronate the mesio-vestibular root of PMS	21 days	Light force
Nakaš et al., 2017 [18] (USA)	10 mMol of clodronate and 2.5 mMol of clodronate injected into the subperiosteal area adjacent to the right maxillary incisor.	3 and 7 days	Not informed
Brunet et al., 2016 [8] (Brazil)	(0.1 mg/kg) of intraperitoneal zoledronic acid	Single dose (One week before experiment)	30 cN
Salazar et al., 2015 [7] (Brazil)	1 mg/kg and 2 mg/kg	90 days	50 cN
Kaipatur et al., 2013 [19] (Canada)	0.015 mg/kg subcutaneously	56 days	50 g
Karras et al., 2009 [20] (USA)	7 mg/kg of body weight of Sodium Alendronate	35 days	50 g
Liu et al al., 2004 [21] (Japan)	2.5,10 and 40 Mm injected into the subperiosteum	21 days	120 mN

Table V - Characteristics related to the experiments

Author/year, country	Experimental unit	Evaluated parameters	Types of analysis
Franzoni et al., 2017 [16] (Brazil)	First molar and third molar upper left, Maxilla	1. Amount of orthodontic movement; 2. Number of blood vessels and fibroblasts; 3. Number of osteoclasts; 4. Number of inflammatory cells.	1. Distance between the distal of the third molar and mesial of the first molar on the left side, measured with digital caliper; 2. Toluidine blue staining method; 3. Toluidine blue staining method; 4. Dominici staining method.
Seifi et al., 2017 [17] (Iran)	First molar and second molar upper left, maxilla	1. Degree of orthodontic movement; 2. Number of blood vessels, osteoblast-like cells and roots resorptive gaps (number and area).	1. Distance between second and first molars using slide gauge; 2. Hematoxylin and light microscope.
Nakaš et al., 2017 [18] (USA)	Upper incisor, first molar on both sides and maxilla	1. Amount of orthodontic movement.	1. Distance between the incisors (middle of the distoproximal surface of the incisors at 2 mm (of the gums) and the molars (the middle of the mesioproximal ridge of the first molar).
Brunet et al., 2016 [8] (Brazil)	First upper right molar and upper central incisor on the same side, maxilla	1. Amount of orthodontic movement; 2. Quantity of osteoclasts; 3. Expression of mature and immature collagen; 4. Presence of hyaline areas and root resorption.	1. Digital caliper positioned at the most cervical point of the tooth measuring the mesial of the first molar to the upper central incisor of the left side by palatine; 2. TRAP staining; 3. Picrosirius; 4. HE.
Salazar et al., 2015 [7] (Brazil)	First and second molars upper right and maxillary	1. Degree of orthodontic movement; 2. Quantification of alveolar bone tissue.	1. Images of the cuts of the first and second molars were captured with an objective of measuring the smallest distance between the distal face of the first molar and the mesial face of the second molar; 2. Slide histology were captured with an objective. The bone located between the mesial and distal root of the first maxillary molar was selected for analysis.
Kaipatur et al., 2013 [19] (Canada)	First and second molars upper right and maxilla	1. Degree of orthodontic movement; 2. Bone renewal rate.	1. Microscope and Optimas software (Media Cybernetics, Newburyport, Mass); 2. Subtherapeutic levels of elemental strontium.
Karras et al., 2009 [20] (USA)	First molar and second molar maxilla	1. Degree of orthodontic movement. 1. Amount of orthodontic movement;	1. Distance between second and first molars using a microscope.
Liu et al., 2004 [21] (Japan)	First and second molars, maxilla	2. Osteoclast count.	1. Distance between first and second molars using profile and tracking projector; 2. Trap method.

with orthodontic treatment influence such events, reducing tooth movement and delaying orthodontic treatment [23,24].

Most of the studies included in this systematic review [7,16,18-21] agreed that the systemic use of bisphosphonates contributed to decrease orthodontic movement. Only the studies by Seifi et al. (2017) [17] and Brunet et al. (2016) [8] disagreed with this negative effect of bisphosphonates, concluding that these drugs did not interfere in the tooth movement process. However, despite not having observed the influence of using bisphosphonate on orthodontic movement, Seifi et al. (2017) [17] found that experimental bisphosphonate significantly inhibited the bone and root resorption in rats, assigning a protective and also beneficial tissue effect to this drug.

For Karras et al. (2009) [20], the inhibitory effect of bisphosphonates on orthodontic movement can be attributed to disrupting osteoclast function and maintaining the compression sites of the periodontal ligament, where bone resorption becomes necessary for tooth movement to occur.

Table VI - Main results and conclusions of the analyzed studies

Author (year, country)	Results	Conclusion
Franzoni et al., 2017 [16] (Brazil)	A reduction of 58.3% in orthodontic movement was observed in the OTM + A Group and 99.6% in the OTM + Z Group when compared to the OTM Group. There was a significant decrease in osteoclast and inflammatory cells in BP treated groups. Blood vessels and fibroblast cells decreased, mainly in the group OTM + Z.	Sodium alendronate and zoledronic acid have similar effects on periodontal tissue during orthodontic treatment in rats. Zoledronic acid may especially reduce orthodontic movement.
Seifi et al., 2017 [17] (Iran)	There were no significant differences in orthodontic movement between the groups of applied force. ZA significantly inhibited bone/root resorption and angiogenesis compared to the positive control group.	Zolena did not decrease orthodontic movement, but significantly inhibited bone and root resorption .
Nakaš et al., 2017 [18] (USA)	In the 7-day interval application regimen, decreased tooth movement was observed with 10 mMol compared to the 2.5 mMol clodronate concentration. However, decreased tooth movement was also observed when 2.5 mMol of clodronate was applied at intervals of 7 versus 3 days. On the other hand, no difference was observed when the concentration of 10 mMol was applied at intervals of 3 to 7 days.	Tooth movement decreases when clodronate is applied subperiosteally in the root area. The tooth movement is impeded by the higher dose of clodronate, as well as by the shorter application interval, even with lower dosage.
Brunet et al., 2016 [8] (Brazil)	A lower number of osteoclasts and a higher percentage of hyaline area were observed in the EAZ group.	There was no difference between the groups regarding bone remodeling, root resorption and tooth movement at all observed times.
Salazar et al., 2015 [7] (Brazil)	Intragroup comparisons showed significant movement after five and seven days ($p < 0.05$) for all groups. The comparison between the groups revealed greater tooth movement in the OVX Group ($p < 0.05$) on day 7.	Both doses of Sodium Alendronate similarly decreased tooth movement in ovariectomized rats ($p > 0.05$). The movement in the ovariectomized groups + alendronate was also lower than the non-ovariectomized groups, but with no statistical difference.
Kaipatur et al., 2013 [19] (Canada)	Both treatment groups with bisphosphonates exhibited reduced tooth movement compared to controls. The bisphosphonate dosage resulted in reductions of 56% and 65% in dental protraction at 4 weeks and 8 weeks, respectively.	The study provided evidence that bone load from the use of bisphosphonates may inhibit orthodontic tooth movement .
Karras et al., 2009 [20] (USA)	Statistical analysis with repeated-measures analysis of variance showed less orthodontic tooth movement in the alendronate group compared with control group (0.06 vs 0.24 mm at 2 weeks, and 0.45 vs 1.06 mm at 4 weeks; $P = 0.0004$ for the alendronate vs control main effect).	This study demonstrated an inhibitory effect of alendronate administration on orthodontic tooth movement in a rat model.
Liu et al., 2004 [21] (Japan)	Local injection of clodronate caused a significant ($P < 0.001$) and dose-dependent reduction in tooth movement in the rats. The number of osteoclasts on the clodronate-injected side was significantly less ($P < 0.01$) than on the control side. Local clodronate also inhibited root resorption incident to tooth movement.	These results suggest that localized use of clodronate could be a useful therapeutic adjunct in orthodontic treatment.

These authors came to this conclusion because they verified that the drug reduced the osteoclasts osteo-resorptive activity when evaluating the effect of alendronate (bisphosphonate type) on the induced tooth movement in rats, resulting in smaller and slower orthodontic movement.

The difference between the findings of some experiments regarding the extent and speed of tooth movement can be attributed to methodological divergences, which seem to have significantly influenced the results. The main variations observed in the methodologies of these studies were related to the usage time of bisphosphonates, which varied between single dose and 90 days of use, and the sample size, varying between 16 and 120 rats [8,21]. Such variations ended up making a real comparison extremely difficult between the experimental results.

Variations in the drug dose also exerted an influence on the results of the studies analyzed, with larger doses associated with smaller and slower orthodontic movements, and smaller doses

associated with larger and faster movements. Corroborating with this statement in investigating the effects of local application of 10mMol bisphosphonate concentrations and 2.5mMol of clodronate on tooth movement at 3- and 7-day intervals, Nakaš et al. (2017) [18] observed that the higher dose of clodronate resulted in a substantially smaller and slower tooth movement.

The magnitude of the forces applied in the studies also varied between 30 and 120 N, resulting in different extensions and speeds of orthodontic movements. Considering that the NiTi spring has the ability to release a force with constant magnitude without declining regardless of the elongation performed, and that heavy forces in rats can cause hyalinization and movement retardation, according to Ren et al. (2004) [25], the ideal for investigation of tooth movement in rats would be to apply a force of less than 10 cN, which may be particularly determinant for analyzing periodontal responses and/or root resorption assessments [25-27].

Another relevant factor is the sex of the animal. Experiments were performed on male rats in most of the studies included in this review. However, female and ovariectomized rats were used in the studies by Salazar et al. (2015) [7], Kaipatur et al. (2013) [19] and Mohammed and Kaklamanos (2021) [28]. These variables should always be considered when comparing results, since the rats present similar behavior to that of postmenopausal women under hormonal conditions, during which they are more prone to osteoporosis and show greater bone remodeling [29].

Although the studies of this review have sometimes shown divergent results, the tools used for their methodological evaluation revealed a low risk of bias even though four information details were not included by the authors; additionally, a frequency of 19.37 was found in the methodological quality, indicating good qualification of the selected studies.

An important limitation of the analyzed studies is that none of them used computerized microtomography (micro-CT) to analyze orthodontic movement. Using micro-CT enables an analysis of several microtomographic planes/sections and the internal three-dimensional visualization of the study material, therefore representing an important resource to offer more reliability to the studies and thus enabling highly accurate and non-destructive data analysis [30]. Another limitation of the analyzed studies was the lack of use of anchoring devices. Only the study by Kaipatur et al. [24] used this device to facilitate orthodontic movement in rats. The purpose of this device is to avoid undesirable reactions and relapses after orthodontic tooth movement. Within this context, it is suggested to carry out more complete additional studies which advance to overcome these limitations in order to bring more reliable results regarding orthodontic treatment.

Although orthodontic treatment is mainly performed on adolescents, an increasing number of adults have sought such treatment. A study by Keim et al. [31] showed that adults comprise 20% of all orthodontic patients, and that number has increased even more in recent years. Considering that bisphosphonates are mainly used by adults and older adults, and that these drugs seem to interfere with orthodontic movement, this paradigm shift points to an increase in the number of adults undergoing orthodontic treatment, and therefore requires a better understanding of the systemic usage effect of bisphosphonates during this treatment.

CONCLUSION

Most studies of this systematic review point to the fact that the systemic use of bisphosphonates during orthodontic treatment seems to reduce the extent and speed of tooth movement, thus extending the treatment duration.

Author's Contributions

GRGL, HSGP: Data Curation. MCM: Conceptualization. MCM: Methodology. GRGL: Writing – Original Draft Preparation. GRGL: Writing – Review & Editing. ECL, RDAUL: Visualization. HSGP: Software. HSGP: Validation. ECL, RDAUL: Supervision. HSGP: Formal Analysis. HSGP: Investigation. HSGP: Resources. ECL, RDAUL: Project Administration and Funding Acquisition.

Conflicts of Interest

The authors declare no conflict of interest.

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Regulatory Statement

Not applicable considering this is a review paper.

References

1. Kapila S, King G. Biologic mechanisms in orthodontic tooth movement. In: Nanda R, editor. Esthetics and biomechanics in orthodontics. Philadelphia: Saunders; 2015. p. 90-107. http://doi.org/10.1016/B978-1-4557-5085-6.00005-9.
2. Roberts W. Bone physiology, metabolism, and biomechanics in orthodontic practice. In: WG Lee, Vig KWL, Huang GJ, Fleming PS. Orthodontics: current principles and techniques. USA: Elsevier; 2012. p. 221-92.
3. Mobile R, Azevedo L, Gomes S, Deliberador T, Giovanini A, Araujo M. The influence of early bisphosphonate treatment in bone reconstruction on craniofacial radiographic bone density. Braz Dent Sci. 2019;22:513-9. http://doi.org/10.14295/bds.2019.v22i4.1747.
4. Poubel VLDN, Silva CAB, Mezzomo LAM, De Luca Canto G, Rivero ERC. The risk of osteonecrosis on alveolar healing after tooth extraction and systemic administration of antiresorptive drugs in rodents: a systematic review. J Craniomaxillofac Surg. 2018;46(2):245-56. http://doi.org/10.1016/j.jcms.2017.11.008. PMid:29233703.
5. Miranda RM, Fernandes JL, Santos MS, Jácome-Santos H, Milagres RMC, Pretti H, et al. Influence of risedronate on orthodontic tooth movement in rodents: a systematic review and case report. Dental Press J Orthod. 2024;28(6):e2322280. http://doi.org/10.1590/2177-6709.28.6.e2322280.oar. PMid:38198389.
6. Fujimura Y, Kitaura H, Yoshimatsu M, Eguchi T, Kohara H, Morita Y, et al. Influence of bisphosphonates on orthodontic tooth movement in mice. Eur J Orthod. 2009;31(6):572-7. http://doi.org/10.1093/ejo/cjp068. PMid:19840975.
7. Salazar M, Hernandes L, Ramos AL, Salazar BO, Micheletti KR, Paranhos LR, et al. Effect of alendronate sodium on tooth movement in ovariectomized rats. Arch Oral Biol. 2015;60(5):776-81. http://doi.org/10.1016/j.archoralbio.2015.02.003. PMid:25766470.
8. Brunet MD, Araujo CM, Johann ACBR, Camargo ES, Tanaka OM, Guariza O Fo. Effects of zoledronic acid on orthodontic tooth movement in rats. Braz Dent J. 2016;27(5):515-23. http://doi.org/10.1590/0103-6440201600966.
9. Choi J, Baek SH, Lee JI, Chang YI. Effects of clodronate on early alveolar bone remodeling and root resorption related to orthodontic forces: a histomorphometric analysis. Am J Orthod Dentofacial Orthop. 2010;138(5):548.e1-8; discussion 548-9. https://doi.org/ 10.1016/j.ajodo.2010.01.031.
10. Fernández-González FJ, Cañigral A, Balbontín-Ayala F, Gonzalo-Orden JM, Carlos F, Cobo T, et al. Experimental evidence of pharmacological management of anchorage in Orthodontics: a systematic review. Dental Press J Orthod. 2015;20(5):58-65. http://doi.org/10.1590/2177-6709.20.5.058-065.oar. PMid:26560822.
11. Krishnan S, Pandian S, Kumar SA. Effect of bisphosphonates on orthodontic tooth movement-an update. J Clin Diagn Res. 2015;9(4):ZE01-5. http://doi.org/10.7860/JCDR/2015/11162.5769. PMid:26023659.
12. Zahrowski JJ. Bisphosphonate treatment: an orthodontic concern calling for a proactive approach. Am J Orthod Dentofacial Orthop. 2007;131(3):311-20. http://doi.org/10.1016/j.ajodo.2006.09.035. PMid:17346585.
13. Rinchuse DJ, Rinchuse DJ, Sosovicka MF, Robison JM, Pendleton R. Orthodontic treatment of patients using bisphosphonates: a report of 2 cases. Am J Orthod Dentofacial Orthop. 2007;131(3):321-6. http://doi.org/10.1016/j.ajodo.2006.11.002. PMid:17346586.
14. Matthew JP, Joanne EM, Patrick MB, Isabelle B, Tammy CH, Cynthia DM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372(71):n71. http://doi.org/10.1136/bmj.n71. PMid:33782057.
15. Michelogiannakis D, Rossouw PE, Al-Shammery D, Akram Z, Khan J, Romanos GE, et al. Influence of nicotine on orthodontic tooth movement: A systematic review of experimental studies in rats. Arch Oral Biol. 2018;93:66-73. http://doi.org/10.1016/j.archoralbio.2018.05.016. PMid:29843070.
16. Franzoni JS, Soares FMP, Zaniboni E, Vedovello M Fo, Santamaria MP, Dos Santos GMT, et al. Zoledronic acid and alendronate sodium and the implications in orthodontic movement. Orthod Craniofac Res. 2017;20(3):164-9. http://doi.org/10.1111/ocr.12192. PMid:28653350.
17. Seifi M, Asefi S, Hatamifard G, Lotfi A. Effect of local injection of Zolena, zoledronic acid made in Iran, on orthodontic tooth movement and root and bone resorption in rats. J Dent Res Dent Clin Dent Prospects. 2017;11(4):257-64. http://doi.org/10.15171/joddd.2017.045. PMid:29354254.
18. Nakaš E, Lauc T, Tiro A, Džemidžić V, Zukanović A, Franić M, et al. Dose- and time-dependent effects of clodronate on orthodontic tooth movement. Bosn J Basic Med Sci. 2017;17(1):23-8. http://doi.org/10.17305/bjbms.2017.1715. PMid:28086064.
19. Kaipatur NR, Wu Y, Adeeb S, Stevenson TR, Major PW, Doschak MR. Impact of bisphosphonate drug burden in alveolar bone during orthodontic tooth movement in a rat model: a pilot study. Am J Orthod Dentofacial Orthop. 2013;144(4):557-67. http://doi.org/10.1016/j.ajodo.2013.06.015. PMid:24075664.
20. Karras JC, Miller JR, Hodges JS, Beyer JP, Larson BE. Effect of alendronate on orthodontic tooth movement in rats. Am J Orthod Dentofacial Orthop. 2009;136(6):843-7. http://doi.org/10.1016/j.ajodo.2007.11.035. PMid:19962607.
21. Liu L, Igarashi K, Haruyama N, Saeki S, Shinoda H, Mitani H. Effects of local administration of clodronate on orthodontic tooth movement and root resorption in rats. Eur J Orthod. 2004;26(5):469-73. http://doi.org/10.1093/ejo/26.5.469. PMid:15536834.
22. Kilkenny C, Browne W, Cuthill IC, Emerson M, Altman DG, NC3Rs Reporting Guidelines Working Group. Animal research: reporting in vivo experiments: the ARRIVE guidelines. Br J Pharmacol. 2010;160(7):1577-9. http://doi.org/10.1111/j.1476-5381.2010.00872.x. PMid:20649561.
23. Allen MR, Erickson AM, Wang X, Burr DB, Martin RB, Hazelwood SJ. Morphological assessment of basic multicellular unit resorption parameters in dogs shows additional mechanisms of bisphosphonate effects on bone. Calcif Tissue Int. 2010;86(1):67-71. http://doi.org/10.1007/s00223-009-9315-x. PMid:19953232.
24. Araújo AS, Fernandes AB, Maciel JV, Santos JN No, Bolognese AM. New methodology for evaluating osteoclastic activity induced by orthodontic load. J Appl Oral Sci. 2015;23(1):19-25. http://doi.org/10.1590/1678-775720140351. PMid:25760264.
25. Ren Y, Maltha JC, Kuijpers-Jagtman AM. The rat as a model for orthodontic tooth movement--a critical review and a proposed solution. Eur J Orthod. 2004;26(5):483-90. http://doi.org/10.1093/ejo/26.5.483. PMid:15536836.
26. Miura F, Mogi M, Ohura Y, Karibe M. The super-elastic Japanese NiTi alloy wire for use in orthodontics. Part III. Studies on the Japanese NiTi alloy coil springs. Am J Orthod Dentofacial Orthop. 1988;94(2):89-96. http://doi.org/10.1016/0889-5406(88)90356-3. PMid:3165245.
27. Gianelly AA, Bednar J, Dietz VS. Japanese NiTi coils used to move molars distally. Am J Orthod Dentofacial

Orthop. 1991;99(6):564-6. http://doi.org/10.1016/S0889-5406(05)81633-6. PMid:2038976.

28. Mohammed AO, Kaklamanos EG. Effect of ovariectomy-induced osteoporosis on the amount of orthodontic tooth movement: a systematic review of animal studies. Eur J Orthod. 2021;43(6):672-81. http://doi.org/10.1093/ejo/cjab013. PMid:33866368.

29. Kubek DJ, Burr DB, Allen MR. Ovariectomy stimulates and bisphosphonates inhibit intracortical remodeling in the mouse mandible. Orthod Craniofac Res. 2010;13(4):214-22. http://doi.org/10.1111/j.1601-6343.2010.01497.x. PMid:21040464.

30 PEDRO RUBEN DAVILA FARIAS. Imagens de micro CT na caracterização de biofilme bacteriano [dissertação]. Rio de Janeiro: Universidade Federal do Rio de Janeiro; 2017.

31. Keim RG, Gottlieb EL, Nelson AH, Vogels DS 3rd. 2009 JCO Orthodontic Practice Study. Part 1 Trends. J Clin Orthod. 2009;43(10):625-34. PMid:20128192.

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