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DOES BISPHOSPHONATE INCREASE THE RISK OF DENTAL PULP AND PERIAPICAL ALTERATIONS? AN EMERGENT CLINICAL CONCEPT FROM A SYSTEMATIC REVIEW

ABSTRACT

Background: Bisphosphonates (BPs) have been linked to in vivo alterations of dental pulp. Therefore, the objective of this systematic review was to evaluate the influence of BP use on the prevalence of dental pulp and periapical alterations. The following section outlines the methodology employed in this systematic review. This systematic review was conducted in accordance with the PRISMA-2020 guidelines and was registered in PROSPERO (CRD42022302614). After screening 1,743 articles in seven scientific databases (PubMed, Lilacs, Livivo, Scopus, Embase, Web of Science, and EBSCO) and three gray literature databases (Open Grey, Google Scholar, and ProQuest), two articles were included. The Newcastle-Ottawa Quality Assessment Scale for Cohort Studies was used to assess the risk of bias (RoB). The results of the study are as follows: The two included articles were cross-sectional and a cohort retrospective study. The cross-sectional study described 13 patients undergoing treatment with zoledronate, with 17 teeth exhibiting dental pulp calcification (65%) or pulp necrosis (76%). The cohort study described 1,644,953 patients, representing a frequency of 0.52% of periapical lesions in the general population. In contrast, the frequency of periapical lesions in the 645 patients who were using Bp was significantly higher at 1.86% (odds ratio = 3.52, CI95% = 3.25-3.82). A meta-analysis was not performed due to the heterogeneity of the outcomes. The cross-sectional study exhibited a high risk of bias, whereas the cohort study exhibited a low risk of bias. Conclusions: This systematic review, which is still in its nascent stages, suggests that blood pressure may be associated with alterations in dental pulp and periapical tissues. Nevertheless, further studies with larger sample sizes and control groups are required.

Keywords: radiotherapy; the term "chemoradiotherapy" is used to describe a specific type of treatment; neoplasms of the head and neck; trismus; quality of life.

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1 INTRODUCTION

Bisphosphonates (BPs) have been extensively studied with regard to their potential to induce osteonecrosis of the jaws. Systematic reviews have addressed the risk factors and therapeutic protocols associated with this condition. However, there has been limited attention given to the potential pulpal changes induced by BPs. These drugs, which have a high affinity for hydroxyapatite, have been shown to cause prolonged inflammatory changes in periodontal tissue (Silva *et al.*, 2017a). Notably, Silva *et al.* (2017b) reported significant alterations in the dental pulp of rats treated with zoledronate, which were linked to dysregulation in the RANKL/OPG axis in the dental pulp (Silva *et al.*, 2019). This axis is crucial for maintaining bone balance and dental biomineralization (Nishida *et al.*, 2021).

Moraes *et al.* (2015) documented significant pulp changes in patients using zoledronate, including hypercementosis, dental ankylosis, pulpal calcification, dentinoid/osteoid formation, and dental pulp necrosis. While descriptive, in vitro and in vivo studies suggest that bisphosphonate treatment disrupts dental pulp metabolism, possibly due to cellular toxicity and inflammatory dysregulation (Silva *et al.*, 2017b, 2019; Cvikl *et al.*, 2011). Consequently, the laboratory findings are translating to clinical outcomes, directing the development of a new concept: does the use of bisphosphonates increase the risk of significant pulp changes? Consequently, the objective of this systematic review is to assess whether the use of bisphosphonates increases the risk of developing pulpal changes.

2 MATERIALS AND METHODS

This study, registered with the number CRD42022302614 in PROSPERO, was conducted in accordance with the PRISMA-2020 checklist.

The PECOS strategy was employed to address the question of whether Bp use increases the risk or prevalence of dental pulp alterations or periapical lesions. A specific search strategy was developed for each database, using relevant keywords such as "Biphosphonates," "Periapical Diseases," and so forth.

The study included cross-sectional and cohort studies that assessed the prevalence of dental pulp alterations or periapical lesions in Bp users. No restrictions were placed on age, sex, ethnicity, or language.

Additionally, case reports, systematic reviews, in vivo/ex vivo/in vitro studies, and articles with incomplete or inadequately described outcomes were excluded.

A comprehensive search was conducted in various databases, including grey literature, up to January 9, 2022.

Two independent reviewers conducted the initial assessment of titles and abstracts in phase 1, followed by a second reviewer evaluating the full texts in phase 2. Any discrepancies were resolved through discussion or the involvement of a third reviewer.

The data extraction was conducted by one author and then cross-checked by another. Discrepancies were resolved through consensus or by a third author.

The study variables included the prevalence of dental pulp alterations and periapical diseases, which were evaluated qualitatively due to the unfeasibility of conducting a meta-analysis.

The Newcastle Ottawa Scale (NOS) was employed to assess the risk of bias, while the GRADE approach was utilized to evaluate the quality of evidence.

The GRADE assessment considered a number of factors, including aspects such as study design, bias, consistency, directness, heterogeneity, precision, and publication bias.

3 RESULTS

METHODOLOGICAL CHARACTERIZATION AND QUALITATIVE ANALYSIS OF STUDIES

A total of 1,743 studies were evaluated in seven scientific literature databases and three gray literature databases. Two

studies were included in this systematic review.

The initial study, a cross-sectional investigation, examined 17 teeth in 13 patients with BRONJ due to zoledronate and alendronate treatment. Among the 1,743 studies evaluated, 12 patients used zoledronate for cancer treatment, while one used alendronate for osteoporosis over one to three years. The findings included hypercementosis (82%), pulp necrosis (76%), dental pulp calcification (65%), dentinoid/osteoid material (18%), and dental ankylosis (6%).

The second study, a retrospective cohort study with a total sample size of 1,644,953, explored periapical lesions in patients with osteoporosis, with one subgroup receiving bisphosphonate treatment. The prevalence of periapical lesions was 0.52%, with osteoporosis patients exhibiting a 3.36-fold higher prevalence than non-osteoporosis individuals. The Bp-treated osteoporosis subgroup exhibited a 2.36-fold higher prevalence than the non-osteoporosis group, while the non-treated osteoporosis subgroup demonstrated a 1.49-fold higher prevalence than the treated one. Alendronate demonstrated a statistically significant increase in periapical lesions (odds ratio 1.61), in contrast to risedronate (p=0.350).

In the two studies reviewed, the cross-sectional study exhibited a high risk of bias (RoB), while the cohort study exhibited a low RoB. Moraes *et al.* (2015). exhibited a lack of representativeness of the exposed cohort and failed to demonstrate comparability and adequacy of follow-up for both cohorts. Conversely, Katz and Rotstein (2021). met all the requisite criteria. The GRADE analysis indicated that the outcomes exhibited a low level of certainty.

4 DISCUSSION

Bisphosphonates have been shown to impact bone metabolism with therapeutic benefits. However, there is a paucity of comprehensive studies investigating their association with pulpal and periapical effects. In their 2019 study, Silva and colleagues proposed that bisphosphonate usage disrupts the RANKL/OPG axis, influencing pulpal changes and dental biomineralization. A systematic review of 1,743 studies identified only two for qualitative analysis, which hindered meta-analysis due to paper heterogeneity.

In their 2015 study on BRONJ patients using zoledronate, Morais *et al.* (2015). observed alterations in the pulpal tissue, including hypercementosis, pulp necrosis, and dental pulp calcification. These findings are consistent with previous studies indicating that zoledronate has an impact on inflammatory mediators and pulp tissue apoptosis (Pourgonabadi *et al.*, 2018; Manolagas, 2000).

A noteworthy observation was the presence of mineralized globules, pulpal stones, and complete obliteration of the pulp chamber in older patients, which challenged conventional expectations (Morse, 1991).

Despite the limitations of the study, the findings offer valuable insights for dentists, particularly endodontists, who can use them to inform case planning and procedures. Nevertheless, further clinical studies on bisphosphonate users are essential for a comprehensive understanding of the medication's effects.

In a 2021 study by Katz *et al.* (2021) on osteoporosis patients taking bisphosphonates, those taking alendronate exhibited a lower prevalence of periapical lesions. Furthermore, our systematic review revealed that the prevalence of pulpal calcifications varies globally, reflecting ethnic heterogeneity.

The prevalence of osteoporosis in postmenopausal women, which is linked to reduced estrogen levels, underscores the importance of maintaining hormonal balance in bone regulation. The downregulation of estrogen has been shown to affect the production of cytokines and growth factors, which may contribute to osteoporotic changes (Li; Wang, 2018; Xiong *et al.*, 2007).

In conclusion, our systematic review establishes a clinical connection between bisphosphonate use and pulpal/

periapical alterations. However, further studies are imperative for a comprehensive understanding and improved patient management.

REFERENCES

CVIKL, B.; AGIS, H.; STÖGERER, K.; MORITZ, A.; WATZEK, G.; GRUBER, R. The response of dental pulp-derived cells to zoledronate depends on the experimental model. **International endodontic journal**, v. 44, n. 1, p. 33-40, 2011.

KATZ, J.; ROTSTEIN, I. Prevalence of Periapical Lesions in Patients with Osteoporosis. **Journal of endodontics**, v. 47, n. 2, p. 234-238, 2021.

LI, L.; WANG, Z. Ovarian Aging and Osteoporosis. **Advances in experimental medicine and biology**, n. 1086, p. 199-215, 2018.

MANOLAGAS, S. C. Birth and death of bone cells: basic regulatory mechanisms and implications for the pathogenesis and treatment of osteoporosis. **Endocrine reviews**, v. 21, n. 2, p. 115-137, 2000.

MORAES, P. C.; SILVA, C. A.; SOARES, A. B.; PASSADOR-SANTOS, F.; CORRÊA, M. E.; ARAÚJO, N. S.; ARAÚJO, V. C. Tooth alterations in areas of bisphosphonate-induced osteonecrosis. **Clinical oral investigations**, v. 19, n. 2, p. 489-495, 2015.

MORSE, D. R. Age-related changes of the dental pulp complex and their relationship to systemic aging. **Oral surgery oral medicine, and oral pathology**, n. 72, v. 6, p. 721-745, 1991.

NISHIDA, D.; ARAI, A.; ZHAO, L.; YANG, M.; NAKAMICHI, Y.; HORIBE, K.; HOSOYA A.; KOBAYASHI, Y.; UDAGAWA, N.; MIZOGUCHI.; T. RANKL/OPG ratio regulates odontoclasto genesis in damaged dental pulp. **Scientific reports**, v. 11, n. 4575, 2021.

POURGONABADI, S.; MOUSAVI, S. H; TAYARANI-NAJARAN, Z.; GHORBANI, A. Effect of zoledronate, a third-generation bisphosphonate, on proliferation and apoptosis of human dental pulp stem cells. **Canadian journal of physiology and pharmacolology**, v. 96, n. 2, p. 137-144, 2018.

SILVA, P. G. B.; FERREIRA JUNIOR, A. E. C.; OLIVEIRA, C. C.; VERDE, M. E. Q. L.; FREITAS, M. O.; SOUSA, F. B.; MOTA, M. R. L.; ALVES, A. P. N. N. Chronic treatment with zoledronic acid alters the expression levels of inflammatory, bone, and apoptotic markers and Toll-like receptors 2 and 4 in rat dental pulp. **Oral surgery, oral medicine, oral pathologic e oral radiology**, v. 128, n. 2, p. 139-145, 2019.

SILVA P. G. B.; FERREIRA JUNIOR, A. E. C.; OLIVEIRA, C. C., BRIZENO, L. A. C.; WONG, D. V. T.; LIMA JÚNIOR, R. C. P.; SOUSA, F. B.; MOTA, M. R. L.; ALVES, A. P. N. N. Chronic treatment with zoledronic acid increases inflammatory markers in periodontium of rats. **Journal of oral pathology & medicine**, v. 46, n. 10, p. 1046-1053, 2017a.

SILVA, P. G. B. *et al.* Immune cell profile of dental pulp tissue treated with zoledronic acid. **International endodontic journal**, v. 50, n. 11, p. 1067-1076, 2017b.

XIONG, H.; PENG, B.; WEI, L; ZHANG, X.; WANG, L. Effect of an estrogen-deficient state and Alendronate therapy on bone loss resulting from experimental periapical lesions in rats. **Journal of endodontics**, v. 33, n. 11, p. 1304-1308, 2007.