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Review

# Influence of bisphosphonates in orthodontic therapy: Systematic review

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ABSTRACT

*Objective:* The objective of this paper was to analyse the effects of bisphosphonates and their influence on orthodontic therapy.
*Data/sources:* The literature was systematically reviewed using PubMed/Medline, Scopus, Ebsco Host, Scirus and Cochrane databases up to December 31, 2008.
*Study selection:* Articles were independently selected by two different researchers based on previously established inclusion and exclusion criteria, finding a good concordance (kappa index of 0.862). The methodological quality of the reviewed papers was assessed. The search strategy identified 205 titles. Thirteen articles were selected after application of the inclusion/exclusion criteria, and only one of these had a high methodological quality. Bisphosphonate applications in orthodontic therapy were divided between two main groups: tooth movement and skeletal relapse.
*Conclusions:* Topical or systemic application of bisphosphonates decreases orthodontic tooth movement and reduces orthodontic tooth movement relapse and skeletal relapse after maxillary expansion or mandibular distraction and similar procedures. Further longer-term studies are required to assess possible adverse effects after bisphosphonate treatment for these purposes.



## 1. Introduction

Bisphosphonates are potent bone resorption inhibitors that are frequently used to treat bone metabolism disorders. There are two types of bisphosphonate: nitrogenous and non-nitrogenous. They act *via* different pathways but both inhibit bone resorption, although their effectiveness differs considerably.[1,2] Nitrogenous bisphosphonates are more potent than those without the nitrogen atom[2] and may inhibit the production of isoprenoid compounds in the mevalonate pathway, thereby preventing protein lipidation, that is, the addition of hydrophobic molecules to the protein. Non-nitrogenous bisphosphonates can be incorporated into adenosine triphosphate (ATP) analogues, and act by inhibit-

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ing protein synthesis and inducing osteoclast apoptosis.[1,3] Induction of osteoclast apoptosis is considered the main action mechanism by which bisphosphonates inhibit bone resorption.[4] Bone is constantly being remodelled even when growth is complete. Bone remodelling is a complex cyclical process in which the osteoclasts resorb the bone mineral matrix and release biomolecular bone-stimulating factors that would otherwise induce stem cells to differentiate into osteoblasts and form new bone. Bisphosphonates attach to bone because of the affinity of their parachlorophenol moiety for hydroxyapatite, and are subsequently phagocytised by the osteoclasts. The incorporation of bisphosphonates by the osteoclast triggers apoptosis (programmed cell death) by competing with ATP or interfering with the 3-hydroxy-3-methyl-glutaryl-Coenzime A reductase (HMG-CoA reductase) pathway.[5] Osteoblast-mediated osteoclastic resorption is described as equally inhibited. Bisphosphonates are incorporated into the bone matrix and can have a half-life of >10 years, implying that the bone metabolism of patients may be affected for many years after pharmacological therapy has ceased.[6]

Various diseases (such as multiple myeloma, bone metastasis, hypercalcaemia and Paget's disease) are treated with intravenous (iv) administration of bisphosphonates,[7,8] decreasing bone remodelling and limiting bone destruction. Furthermore, since bisphosphonates are shown to have improved the clinical outcome in osteogenesis imperfecta,[9] they are very commonly used to treat this disease that affects dentinogenesis in several of its subtypes. Oral administration is largely indicated to treat osteoporosis and peri- and post-menopause osteopenia,[10] which are characterized by a decrease in bone density and subsequent fragility and propensity to fracture.

Bisphosphonates have been reported as possessing anti-angiogenic properties. The accumulation of high concentrations of these compounds in bone tissue has been shown to inhibit endothelial proliferation and reduce capillary formation.[11,12] The over-accumulation of bisphosphonates in alveolar bone may result in the reduction of endothelial cells and capillary neoformation, establishing a predisposing condition for the development of avascular osteonecrosis.[13] Intravenous and chronic oral bisphosphonate administration have been associated with osteonecrosis of the maxillary bones,[14] and there have also been reports of oesophagitis and mucosal ulcerations in relation to oral bisphosphonate treatment.[14] In most cases, bisphosphonate-related osteonecrosis is secondary to dental extraction procedures, periodontal disease or mucosal trauma,[15] although it may also arise spontaneously.[16] The American Society of Bone and Mineral Research has issued a consensus document,[17] one of whose conclusions, among others, was that the risk of osteonecrosis was higher in cancer patients treated with high doses of intravenous bisphosphonates than with oral bisphosphonate therapy.

There are numerous references in the literature to the use of bisphosphonates with dental patients in general,[18] and orthodontic patients in particular.[19] The main purpose of this systematic review was to analyse the available scientific evidence about the effect of bisphosphonate application in orthodontic therapy.

## 2. Materials and methods

### 2.1. Search strategy

The search strategy followed the indications of the *National Health Service Centre for Reviews and Dissemination*,[20] exploring the Medline database (Entrez PubMed, www.ncbi.nim.nih.gov) for papers published between 1953 and December 31, 2008. The key MeSH (Medical Subject Headings) terms used were: "*diphosphonates*" or "*bisphosphonates*" combined with "*orthodontics*" or "*tooth movement*". The search was expanded by including the following databases: Scopus (from 1966 to December 31, 2008), Ebsco Host (from 1997 to December 31, 2008), Scirus (from 1966 to December 31, 2008), and Cochrane (from 2001 to December 31, 2008), using the key words *bisphosphonates* and *diphosphonates* combined with *orthodontics*, *tooth movement*, *corrective orthodontics*, *orthodontic anchorage procedures* or *orthodontic appliances*. Selected article references were reviewed in order to extend the search for relevant articles.

### 2.2. Selection critera

Inclusion criteria were:

1. Experimental animal study, clinical or *in vitro* investigation including at least one experimental group and one control group.
2. Minimum of five animals or samples per experimental group.
3. Systemic or topical administration of bisphosphonate.
4. Description of administration dose and regimen.
5. Application of force by orthodontic or orthopaedic device.
6. Description of direction and magnitude of the force.
7. Appropriate data analysis.
8. English language.

We excluded case reports, case series, descriptive studies, review articles, opinion articles, letters, and articles that did not correspond to the objectives of this review.

### 2.3. Data gathering and analysis

The initial selection of articles was based on title and abstract, with a review of the complete article whenever there was any doubt as to whether to include it or not. Two reviewers (A.I.L. and R.Y.V.), independently applied the inclusion and exclusion criteria to every article, with good concordance being shown (kappa index, 0.862). Studies were classified and stored by: main author, publication year, study design, sample size, type of bisphosphonate and administration, bisphosphonate concentration and dose, type of force (expansion or contraction) and amount of force, tests conducted and conclusions. Data were independently extracted by each reviewer, with intraexaminer conflicts being resolved by discussing the article in question until consensus was reached.

The methodological quality of the selected papers was assessed by using a modified version of the method reported by Antczak et al.[21] and Jadad et al.[22] The following characteristics were considered: sample size, previous estimation of