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# Isotretinoin and Orthodontic Tooth Movement- A Review of the Literature

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## ABSTRACT

*Retinoids, derivatives of vitamin A, play a crucial role in various physiological processes, including vision, immune function, bone mineralization and cellular differentiation. Isotretinoin (13-cis-retinoic acid), a powerful retinoid is widely used in treating severe acne, particularly in adolescents and young adults. As the patient population experiencing the onset of severe acne coincides with the largest patient age group requesting orthodontic treatment, the impact of isotretinoin on bone metabolism raises concerns. This manuscript reviews the mechanism of action of isotretinoin and its effects on bone and the implications for orthodontic tooth movement in clinical practice.*

## Keywords

Isotretinoin, Orthodontic Tooth Movement, Food and Drug Administration (FDA).

## Introduction

Isotretinoin, also known as 13-cis-retinoic acid, is an isomer of tretinoin, the oxidized form of vitamin A. Approved by the U.S. Food and Drug Administration (FDA) in 1982, it is primarily prescribed for the treatment of severe, resistant, nodular acne that does not respond to conventional therapies, including systemic antibiotics. As an oral prescription medication, isotretinoin is a potent retinoid that targets the sebaceous glands by binding to specific retinoid receptors and modifying gene transcription [1]. This mechanism reduces the activity and size of the sebaceous glands, thereby decreasing sebum production. While highly effective in treating acne, long-term use of isotretinoin can significantly impact bone health, being associated with reduced bone mineral density, particularly in the spine and hips, which increases fracture risk. In adolescents, isotretinoin can cause premature closure of the epiphyseal growth plates, leading to stunted growth [2]. Additionally, some users experience bone pain or abnormal bone growth (hyperostosis), which may persist even after discontinuing the medication [3]. Beyond its dermatological effects, isotretinoin interferes with vitamin D metabolism and antagonizes its role in calcium homeostasis, further complicating bone health. In very recent animal studies, an overdose of vitamin A has been shown to accelerate bone resorption by increasing osteoclast activity, underscoring the potential risks isotretinoin poses to bone remodeling [4,5]. This interference is particularly important to explore in the context of orthodontic treatment. However, there is a lack of literature regarding reports of intraoral alterations in patients during isotretinoin treatment. The aim of this paper is to review the effects of isotretinoin on orthodontic tooth movement considering recent findings.

## Mechanism of Action of Isotretinoin

The mechanism of action of isotretinoin is thought to be similar to all-trans-retinoic acid; the active metabolite of Vitamin A [6]. Retinoic acid interacts with nuclear receptor binding sites affecting DNA transcription and protein expression. Retinoid receptors are found in numerous cells such as liver, kidney, and bone tissue. The 13-cis retinoic acid molecule undergoes some isomerization to all-trans-retinoic acid but does not have the same affinity for nuclear retinoic acid receptors [6]. The unique mechanism of isotretinoin may have some intrinsic effect on DNA transcription that has not been described in literature; however, it is unclear what proportion of the isotretinoin effect on the body is due to isomerized retinoic acid.

Osteogenesis in the growth of long bones depends on the action of endogenous retinoids to promote and maintain chondrocyte maturation. Endogenous retinoids, chiefly all-trans-retinoic acid, enter the cytosol of chondrocytes and regulate the processes of terminal differentiation that lead to the deposition of bone on the existing cartilaginous matrix [7]. The signal for beginning the process of endochondral ossification is triggered by the retinoid-induced expression of type X collagen in the hypertrophic zone in the epiphyseal region of long bones. This specialized signal to begin osteogenesis is also joined with transcription factor RUNX2, the action of thyroid hormones, androgen production, and members of the transforming growth factor superfamily [8]. Wang and Kirsch [9] also demonstrated that mature chondrocytes under the influence of all-trans-retinoic acid produce large quantities of annexins type II, V, and VI. These proteins embed themselves in the phospholipid membrane and form channels that trigger an influx of Ca2+ prior to matrix calcification thus underscoring the role of retinoic acid in bone formation [7,9]. Therapeutic amounts of exogenous 13-cis-retinoic acid administered for a period of 6 months have been shown to cause chondrocyte hyper-maturation during endochondral ossification leading to reports of premature epiphyseal closure in children [10-12]. These findings are consistent with the proposed effect of administering all-trans-retinoic acid for the same time period.

Other changes in mineralized tissue have also been documented with the use of isotretinoin. Hyperostotic changes have been reported over 30 years ago in patients who were administered an average of 2.0mg/kg/day with radiographic change present after 6 months of treatment [13]. In 2011, Bergoli et al. studied the effect of isotretinoin on alveolar repair in rats after exodontia. Daily doses of 7.5mg/kg of body weight per *os* of isotretinoin were reported to increase bone repair via accelerated epithelial cellular differentiation and maturity as well as increased deposition of new compact bone [14].

Despite compelling data that supports the hypothesis that isotretinoin administration causes an increase in bone formation and repair, osteolytic changes have also been documented after the administration of 13-cis-retinoic acid. Very early studies showed that increases in dietary Vitamin A can cause bone demineralization that can lead to fracture [15]. Isotretinoin administration has been documented to cause a transient decrease in serum calcium with a compensatory rise in parathyroid hormone with normal serum calcium levels returning to baseline values within 2 weeks [16]. That study by Kindmark could not explain the reason why isotretinoin caused a temporary drop in markers of bone turnover in acne patients [16]. Wang and Kirsch's work in 2002 [9] describing the formation of an annexin mediated calcium channel which would trigger an influx of calcium into the cell thus causing a decrease in serum calcium that would be corrected by compensatory mechanisms.

Interestingly, isotretinoin is known to cause both osteoporosis and hyperostotic changes resembling diffuse idiopathic skeletal hyperostosis (DISH) [17]. Early studies have suggested that high-dose, long-term isotretinoin treatment may cause demineralization and osteoporosis [17,18]; however, conflicting results have been reported in studies evaluating changes in bone mineral density (BMD) with short-course isotretinoin therapy for acne [19]. Leachman [20] showed that bone density at Ward's triangle decreased a mean of 4.4% after 6 months of oral isotretinoin compared to healthy age and gender matched subjects. In a multicenter study, DiGiovanna et al. [21] investigated the effects of isotretinoin therapy on BMD in 217 patients with severe, recalcitrant, nodular acne and reported similar findings. Although DiGiovanna et al. [21] and Leachman et al. [20] found a decrease in BMD in Ward's triangle of the hip, Ward's triangle can be affected by positional changes and is not considered suitable for evaluating BMD. Indeed, the World Health Organization recommends that the total BMD values obtained from at least two different locations should be considered in order to diagnose osteoporosis [22].

## Clinical Relevance of Isotretinoin

The drug 13-cis-retinoic acid is a member of the retinoid family which includes compounds structurally similar to Vitamin A. Retinoids influence various phases of cellular differentiation, mineralization events, as well as protein synthesis, cell signaling, and apoptosis.

Isotretinoin has been shown in the literature to modulate keratinocyte maturation and adhesion and to reduce the size and production of sebum secreting glands [23]. Due to its effectiveness, isotretinoin is the most widely used medication for treatment of recalcitrant acne vulgaris and often has a curative effect after 4-6 months of treatment [24,25].

The standard regimen of 13-cis-retinoic acid for *acne vulgaris* consists of a dosage of 0.5mg - 2mg/kg/day until major outbreaks subside, generally after 4-6 months. Because orthodontic tooth movement depends on cell signaling as well as repair and remodeling of mineralized tissue, a 4-6 month course of isotretinoin could modulate otherwise predictable orthodontic therapy. The most serious side effect of isotretinoin is its action as a teratogen with other side effects appearing like those reported with hypervitaminosis A [26].

While it has not been established if young adults receiving a short course of low-dose isotretinoin therapy for the treatment of acne have had any damaging effect on bone mineral density [27]. The clinical significance of secondary effects of isotretinoin therapy has yet to be determined. Isotretinoin is most prescribed to young adults who are actively growing and where disturbances in bone mineralization could have detrimental long-term effects. Young adults are also the group most likely to initiate orthodontic treatment for the correction of various malocclusions. The symptoms of Vitamin A toxicity include reduced bone mineral density, calcification of tendons and ligaments, and premature epiphyseal closure. While Nishio et al., [28] showed no significant difference in the rate of orthodontic tooth movement and bone

volume between control and experimental groups, their study revealed that the alveolar bone of the isotretinoin group contained more medullary spaces with inflammatory, hematopoietic cells, blood vessels and intense immunolabeling for VEGF-C. An earlier study by Ertugrul et al. [29] also showed that isotretinoin influences vitamin D metabolism by antagonizing the role of this vitamin in calcium homeostasis. Their study also suggests that the ability of isotretinoin to affect mineralized tissue does so in a time and dose dependent manner.

### The Effects of Isotretinoin on the Orthodontic Tooth Movement Process

Orthodontic tooth movement relies on a cascade of inflammatory responses triggered by the forces generated by orthodontic appliances. This process involves the remodeling of the alveolar bone, changes in the periodontal ligament, and sometimes alterations in the root cementum. When teeth move during orthodontic treatment, the process primarily involves a coordinated cycle of bone resorption on the pressure side of the tooth and bone deposition on the tension side. This allows the tooth to gradually shift into its new position; this dynamic process is called bone remodeling and is facilitated by osteoclasts (for resorption) and osteoblasts (for deposition). Thus, conventional tooth movement results from biological cascades of resorption and apposition caused by the mechanical force provided by orthodontic appliances. The rate of orthodontic tooth movement depends on the magnitude, direction, and duration of forces as well as other physiological factors. The direct effect of such forces is a reversible deformation or strain in the tooth and its surrounding tissues, including the periodontal ligament (PDL) and the alveolar bone. Application of force will result in reversible hyalinization of the PDL due to both anatomical and mechanical factors [30,31]. The histologic changes act as a marker of the biological response to orthodontic forces. Previous studies have indicated that hyalinized areas, which are indicative of tissue remodeling, appear around the third day of induced tooth movement and gradually decrease thereafter [4]. The timing of this process impacts the overall rate of tooth movement, as the transition from hyalinization to active remodeling influences how quickly and efficiently the tooth can be moved.

A very recent study by Gok et al., [32] suggests that isotretinoin causes root resorption independent of orthodontic force. Their study, however, was unable to show a significant difference in orthodontically induced tooth movement that could be attributed with isotretinoin treatment. Since isotretinoin affects vitamin D metabolism and bone remodeling, it can impact these cellular events, leading to changes in both the quality and quantity of tooth displacement during treatment. The retinoid may disrupt the balance between osteoblasts (bone formation) and osteoclasts (bone resorption), delaying or complicating orthodontic tooth movement. In adolescents, premature closure of growth plates could hinder jaw development, leading to misalignment or stunted growth, which can affect orthodontic outcomes. With this, isotretinoin is mainly used among adolescents and young adults and coincidentally the same age group that undergoes orthodontic treatment. For these reasons, understanding isotretinoin's effects on bone metabolism is essential when planning orthodontic treatment, especially in younger patients.

## Conclusion

The effects of isotretinoin on bone metabolism are dose-dependent, with higher dosages leading to bone structure displacement and alterations in bone morphology. Such findings in the literature could suggest that higher doses for a longer period may have an effect on orthodontic treatment. The implications for clinical practice are profound; careful monitoring of adolescents undergoing isotretinoin treatment is essential to mitigate risks associated with orthodontic therapy. Interprofessional collaboration between dermatologists and orthodontists may be warranted to optimize treatment outcomes while considering the potential adverse effects of isotretinoin. This manuscript underscores the need for ongoing research and careful consideration in the management of orthodontic patients treated with isotretinoin, highlighting the delicate interplay between pharmacology and dental biomechanics.


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