The Use of Bisphosphonates in Increasing Bone Mineral Density and Decreasing Fracture Occurrence in Children with Osteogenesis Imperfecta

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The Use of Bisphosphonates in Increasing Bone Mineral Density and Decreasing Fracture Occurrence in Children with Osteogenesis Imperfecta

Abstract
Background: Osteogenesis imperfecta (OI) is a heritable disease marked by a varying degree of low bone mass and increased incidence of fractures. Approximately 1 in 15,000 and 1 in 20,000 children are affected by this connective tissue disorder. Although, the mainstay of treatment for children and adolescents with OI is multidisciplinary, the role of bisphosphonates is rapidly becoming the standard of care. Bisphosphonates work by inhibiting osteoclast mediated bone resorption, therefore, allowing osteoblast more time for bone formation. Currently, very little is known about the effect of oral bisphosphonate treatment; despite it being under investigation in controlled trials. This can be attributed to the lack of blinding and relatively small study populations in previous reviewed studies. Therefore, the purpose of this systematic review is to determine the efficacy of bisphosphonates in increasing bone mineral density and decreasing the incidence of fractures in a larger study population with adequate blinding in randomized control trials.

Methods: An exhaustive literature search was performed in the following databases Medline-Ovid, CINAHL, Web of Science, and Medline-PubMed. The keywords include “osteogenesis imperfecta,” “children,” and “bisphosphonates.” Articles selected were limited to those studies in the English language, studies with a publication date in or after 2010, randomized control trials and a study population greater than 100 participants.

Results: Two articles met inclusion criteria. The first study included was a randomized, double-blind, placebo-controlled study with 143 participants who demonstrated that risendronate was effective in both decreasing the incidence of fractures and increasing bone mineral density. The second study was a prospective, randomized, double-blind, parallel-group, placebo-controlled study with 139 participants. This study concluded that alendronate increased bone mineral density but did not decrease the incidence of fractures.

Conclusion: Largely, this conflict in opinion is the reason bisphosphonates are in great debate for the treatment of OI. It is essential to come to a consensus on whether or not bisphosphonates remain an adequate and safe treatment option for children with OI. The evidence presented in this paper proves that bisphosphonates are useful in increasing BMD, but the evidence on decreasing incidence of fractures remains inconclusive, indicating further research is necessary.

Keywords: osteogenesis imperfecta, children, bisphosphonates

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Keywords
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Subject Categories
Medicine and Health Sciences

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Biography

[Redacted for privacy]
Abstract

Background: Osteogenesis imperfecta (OI) is a heritable disease marked by a varying degree of low bone mass and increased incidence of fractures. Approximately 1 in 15,000 and 1 in 20,000 children are affected by this connective tissue disorder. Although, the mainstay of treatment for children and adolescents with OI is multidisciplinary, the role of bisphosphonates is rapidly becoming the standard of care. Bisphosphonates work by inhibiting osteoclast mediated bone resorption, therefore, allowing osteoblast more time for bone formation. Currently, very little is known about the effect of oral bisphosphonate treatment; despite it being under investigation in controlled trials. This can be attributed to the lack of blinding and relatively small study populations in previous reviewed studies. Therefore, the purpose of this systematic review is to determine the efficacy of bisphosphonates in increasing bone mineral density and decreasing the incidence of fractures in a larger study population with adequate blinding in randomized control trials.

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Table I: GRADE profile: Bisphosphonate use in increasing BMD and decreasing reoccurrence of fractures in children with OI.

List of Abbreviations

OI…………………………………………………………………………………Osteogenesis Imperfecta
BMD………………………………………………………………………………Bone Mineral Density
CI………………………………………………………………………………Confidence Interval
The Use of Bisphosphonates in Increasing Bone Mineral Density and Decreasing Fracture Occurrence in Children with Osteogenesis Imperfecta

BACKGROUND

Osteogenesis imperfecta (OI) is a rare heritable disease of connective tissue affecting between 1 in 15 000 and 1 in 20 000. Characteristics of OI include a varying degree in low bone mass and increased susceptibility of fractures. Additionally, patients with OI may experience muscle weakness, hearing loss, fatigue, joint laxity, scoliosis, blue sclera, dentinogenesis imperfecta or brittle teeth, short stature and even restrictive pulmonary disease. Some patients have considerable skeletal deformity with normal sclera and others have little deformity and very blue sclera. A small portion of patients will not survive infancy.

The majority of cases of OI are a result of disturbances in the formation of type 1 collagen. Type 1 collagen fibers play a large role in the ductility and toughness of bone. Most cases of OI are inherited as autosomal dominant and are a result of a mutation in a gene that encodes for type 1 collagen. The majority of those with OI, around 90% in fact, have a mutation in either COL1A1 or COL1A2.

A review conducted in 1979 was performed to distinguish genetic heterogeneity of OI and to determine the relationship between surviving and lethal cases. This review performed by Sillence et al was conducted in Victoria, Australia. The authors confirmed that there are at least four types of OI. Type I was found to be autosomal dominant and relativity mild. This is the most common form of OI, it comprises about 50% of the population with OI. It consists of normal or slightly short stature, little to no bone deformity, blue sclera, ligament laxity, hearing loss and dentinogenesis imperfecta. Type
II, autosomal recessive in inheritance is the most lethal form of OI. Pronounced deformities, multiple fractures at birth and underdeveloped skull attribute to the lethality of this type. Type III also autosomal recessive is severe in nature. It is associated with fractures at birth, short stature, severe scoliosis, triangular facies, grey sclera and dentinogenesis imperfecta. Lastly, type IV is autosomal dominant and is moderately severe. Short stature, scoliosis, white or grey sclera and dentinogenesis imperfecta are associated with this type. The Sillence classification has been expanded to encompass type V and type VI. These two types are not associated with type 1 collagen, but are treated similarly as the other types.¹⁻³ This classification is accepted and widely used today in the diagnosis of OI.

The mainstay of treatment for children and adolescents with OI is multidisciplinary involving physiotherapy, rehabilitation and orthopedic surgery. It is of no surprise that bisphosphonates are rapidly becoming a standard of care.⁴ For more than three decades, bisphosphonates have been used for multiple skeletal disorders.⁵ Bisphosphonates can offer clinical benefit in conditions with imbalances between osteoblast-mediated bone formation and osteoclasts-mediated bone resorption.⁵ Bisphosphonates have a high affinity for bone mineral because they bind to hydroxyapatite crystals. Therefore, bisphosphonates skeletal retention is dependent on the availability of hydroxyapatite binding sites. Bisphosphonates are incorporated into these sites during active bone remodeling, which occurs in conditions leading to accelerated bone turnover. Also, by inhibiting osteoclast mediated bone resorption, bisphosphonates allow bone-forming osteoblast more time for bone formation. Although, bisphosphonate
therapy is well established for children with OI, data is limited in terms of efficacy and risk of harm.\textsuperscript{5}

Currently very little is known about the effect of oral bisphosphonate treatment, despite it being under investigation in controlled trials.\textsuperscript{6} A systematic review\textsuperscript{7} conducted in 2009 on nine studies, revealed multiple limitations in determining the efficacy of bisphosphonates when related to incidence of fractures and increasing bone mineral density. A major limitation discussed in the review, was focused on the small sample size of each study. As stated in the review the largest sample size was 64 participants. Another limitation noted in the review was that five of the nine studies were not blinded.\textsuperscript{7} The purpose of this systematic review is to analyze data that had been established after 2009, with larger study populations and blinding.

**METHODS**

An exhaustive literature search was performed in the following databases Medline-Ovid, CINAHL, Web of science, and Medline-PubMed. The keywords utilized to perform the search include “osteogenesis imperfecta,” “children,” and “bisphosphonates.” Selection of articles was based on an inclusion and exclusion criteria.

Articles selected were limited to those studies in the English language, studies with a publication date in or after 2010, randomized control trials and a study population greater than 100 participants. Grading of Recommendations, Assessment, Development and Evaluations (GRADE) was used to assess the quality of each of the articles reviewed.\textsuperscript{8}
RESULTS

Initially, a comprehensive search yielded a total of 71 articles. After careful review a total of two articles \(^9,^{10}\) met the inclusion and exclusion criteria. Both articles selected were randomized control trials, conducted in or after 2010, with a study population of greater than 100 participants. See Table I.

Bishop et al\(^9\) conducted an international, randomized, double blind, placebo-controlled study to determine if the use of risendronate, a bisphosphonate, was an effective treatment for children with OI. A total of 147 patients were enrolled at 20 hospital centers across 13 countries. Patients were stratified into two groups based on age, one group with an age range of 4-9 and the other 10-15 years old. The groups were then randomly assigned to either receive treatment or placebo by a telephone based interactive voice response system in a 2:1 ratio. The risendronate and placebo tablets were identical in appearance. The study investigators, patients and the center personnel were all blinded during the first 12 months. After 12 months all patients received the study medication in an open label phase. The open label phase was conducted for an additional two years.\(^9\)

The inclusion criteria consisted of children with OI from the ages of 4-15 years. Eligibility was based on a history of at least one non-traumatic or low impact fracture and an age-adjusted and sex-adjusted areal bone mineral density (BMD) Z score of -1.0 or less. Patients were excluded if they weighed less than 10 kg, had a history of cancer within the last five years, had untreated rickets during the previous year, had a serum 25-hydroxyvitamin D concentration of less than 20 nmol/L, had previous treatment that could affect the results of the study or had disease severe enough to warrant the use of intravenous bisphosphonates.\(^9\)
The patients were dosed according to weight. Patients who weighed 10-30kg received 2.5mg risendronate or placebo daily. Those who weighed more than 30kg received 5mg of risendronate or placebo daily. The demographics and disease characteristics were similar between the two groups. The lumbar spine BMD between the two groups was also similar, but differed in their total body BMD. The risendronate group had a total body BMD Z score of -1.42 and the placebo group total body BMD Z score of -1.82.9

The primary endpoint was the percentage change from baseline in lumbar spine areal BMD after 12 months. This outcome was assessed using dual-energy x-ray absorptiometry of the lumbar spine and total body at months 6, 12, 24 and 36. The secondary endpoint consisted of multiple outcomes, such as the incidence and rate of new vertebral and non-vertebral fractures, as well as percentage change from baseline in bone turnover markers. Although multiple outcomes were assessed as a secondary endpoint, of interest in this review is the incidence of new non-vertebral fractures. New non-vertebral fractures were confirmed based on symptoms and radiograph findings.9

After randomization was complete, 94 patients were assigned to the risendronate group and 49 patients were assigned to the placebo group. The mean percentage increase in spine BMD after one year was 16.3% (95% CI 14.4-18.2) in the risendronate group and 7.6% (95% CI 5.1-10.1) in the placebo group. A p value of <0.0001 was calculated. After the first year, when both groups received the risendronate, increases of lumbar spine BMD were similar in the two groups. In the placebo-control phase, non-vertebral fractures were confirmed in 29 (31%) of the 94 participants in the treatment group and 24 (49%) of the 49 participants in the placebo group. A calculated p value of 0.0446 was
noted. The relative risk ratio of 0.63, which resulted in a 39% reduction of fractures, was determined and the number needed to treat was 6. After 12 months, risendronate was found to reduce the risk of recurrent fractures by 42% (HR 0.58, 95% CI 0.4-1.0) with a calculated p value of 0.0416.

The authors determined that oral risendronate increased BMD and reduced the risk of recurrent fractures. In addition, the authors recommend the use of risendronate as a valid treatment option for children with osteogenesis imperfecta.

Ward et al conducted a prospective, randomized, double-blind, parallel-group, placebo-controlled, multicenter study. The study focused on the efficacy and safety of daily oral alendronate in children with osteogenesis imperfecta. Children and adolescents with OI were recruited at 16 Shriners hospitals in North America. Patients were randomized in a 3:1 ratio to alendronate and placebo groups. They were then stratified according to weight. Those that were 40kg or less received 5mg daily of alendronate. Individuals greater than 40kg received 10mg of alendronate. The placebo was identical in appearance despite the differences in dosage.

The inclusion criteria included children, both males and females, ages 4-18 years old. Patients were required to have had a diagnosis of type III or IV OI. If patients were diagnosed with type I, they must have had one or more of the following associated symptoms: chronic pain, more than three fractures per year, minimal trauma for the previous 2 years, or a limb deformity requiring surgery. Patients were excluded if they were unable to comply fully with the dosing instructions, had previously received treatment with a bisphosphonate, or were regularly using drugs that altered gastric acidity.
Baseline characteristics between the two groups were similar. Lumbar spine BMD z score was -4.50 ± 1.45 in the alendronate group and -4.56 ± 1.61 in the placebo group. The number of lifetime fractures across the two groups was 51.6 ± 70.8 in the treatment group and 40.6 ± 53.6. Also, similar between groups was the number of fractures reported during the year before the study. There were 2.0 ± 3.0 in the alendronate group and 2.6 ± 2.6 in the placebo group.10

The primary endpoint of this study was the change in lumbar spine areal BMD z-score. To assess this, dual-energy x-ray absorptiometry was performed at baseline and at 6 months intervals. The scans were then analyzed at a central facility. The results were converted to age and sex-specific z scores using data provided by the manufacturer. The secondary endpoints were cortical width at the midpoint of the second metacarpal as determined by radiographs, the number of radiologically confirmed fractures, the number of investigator-reported fractures and the change in cortical width of the iliac bone determined by transiliac biopsy. The focus of this review is aimed at the number of fractures during the course of this two year study. This endpoint was assessed in two ways. The first method was performed by obtaining radiographs of the upper extremity long bones and lower extremity long bones at baseline and at yearly intervals. The radiographs were assessed for evidence of fractures by three blinded radiologist. The determination of present fractures must have been unanimous. Fractures determined in this manner were titled radiologically confirmed fractures. The second method was reported by the parent or guardian of the patients. The fractures were not necessarily confirmed by radiographs, but were recorded at each study visit by the investigator. Fractures identified in this manner were titled investigator-reported fractures.10
A total of 139 patients with OI were randomized. Twenty six patients in the alendronate group and four patients in the placebo group discontinued. Discontinuation was due to loss to follow-up, adverse events, withdrawn consent and protocol deviation. After factoring out the patients that discontinued the study, 83 patients in the alendronate group and 26 patients in the placebo group completed the two year study. At the completion of the study lumbar spine areal BMD was significantly increased in both alendronate and placebo groups. In the alendronate group, BMD increased by 51% and 12% in the placebo group. The lumbar spine BMD Z score in the treatment group increased from -4.6 to -3.3, a p value of <0.001, revealing a significant improvement. On the other hand, the z scores in the placebo group went from -4.5 to -4.6, a rather insignificant increase. When assessing the incidence of fractures that were radiologically confirmed by month 24, there was little difference between the two groups. In the alendronate group there was 1.96 with a 95% CI of 1.40-2.75. In the placebo group the incidence of fractures was 1.75 with a 95% CI of 1.10-2.80, a calculated p value of 0.614.10

According to the authors, they found that oral alendronate over a course of 24 months was effective in increasing lumbar spine areal BMD z score over placebo. They also concluded, there was no significant effect of alendronate on the incidence of fractures.10
DISCUSSION
Objectives of this systematic review include the efficacy of bisphosphonates for increasing bone mineral density and decreasing incidence of fractures. Although bisphosphonates have been studied extensively, it is evident that the true efficacy and long term effects are not well known, especially when it comes to children suffering with OI. Adverse effects of bisphosphonates are not to be taken lightly; osteonecrosis of the jaw, hypocalcemia, oversuppression of bone turnover and atrial fibrillation are all serious side effects. Thus, it is imperative to weigh both the risks and benefits when using this treatment in a population as delicate as children.

Bishop et al concluded that oral risendronate increased bone mineral density and decreased the incidence of fractures. In terms of blinding and randomization this study has proven to be well done, but it is not without limitations. One limitation that jeopardizes its validity significantly is the inconsistency between the control and treatment groups. In other words, the prognostic variables at baseline were not similar. To restate the facts, the treatment group baseline total body bone mineral density z-score was -1.42 and in the placebo group it was -1.82. This is a significant difference and affects the validity of the study to a great degree. It is undoubtedly so, the treatment group had an overall better result when compared to the placebo group since it had a much better prognosis at baseline. Despite the differences in total body BMD at baseline, groups were otherwise prognostically balanced. For instance, when considering lumbar spine BMD, groups were nearly identical; with a z score of -2.130 in the treatment group and -2.120 in the placebo group.
In comparison, the study performed by Ward et al\textsuperscript{10} lumbar spine BMD was also similar between the two groups at baseline. This study did not analyze total body BMD, therefore, it is difficult to determine if the two groups were more prognostically balanced at baseline than in the study conducted by Bishop et al.\textsuperscript{9}

Of importance, Ward et al\textsuperscript{10} concluded that alendronate increased lumbar spine BMD but was not associated with decreased fracture outcomes. Both studies agreed that bisphosphonates increase BMD, but differ when it comes to incidence of fractures. This could be for many reasons. One reason could be that both studies were different in terms of length. Bishop et al\textsuperscript{9} was one year and Ward et al\textsuperscript{10} was two years. It is possible within the first year of treatment, incidence of fractures improve but later plateau yielding little to no effect. Another reason can be attributed to the difference in the type of bisphosphonate. Bishop et al\textsuperscript{9} used the treatment drug oral risendronate and Ward et al\textsuperscript{10} used oral alendronate. Both study medications are third generation bisphosphonates,\textsuperscript{5} it is possible that a slight alteration in chemical structure could lead to a difference in treatment effect. The last possibility for differences in results could be attributed to the severity of the disease. Ward et al\textsuperscript{10} had an overall study population with a greater amount of participants with OI type III and IV, the more severe of the phenotypes. To be exact, Ward et al\textsuperscript{10} had a total number of participants with Type III OI of 39 in both treatment and placebo groups combined. Whereas, Bishop et al\textsuperscript{9} had five study participants with Type III in both treatment and placebo groups combined. This is a significant difference in the severity of disease across both studies. With the numerous differences accounted for across both studies, it is evident why, in fact, both studies concluded in a difference in opinion.
CONCLUSION

Largely, this conflict in opinion is the reason bisphosphonates are in great debate for the treatment of OI. As medical providers and researchers it is essential to come to a consensus on whether or not bisphosphonates remain an adequate and safe treatment option for children with OI. The evidence presented in this paper proved that bisphosphonates are useful in increasing BMD, but the evidence on decreasing incidence of fractures remains inconclusive.
References


**TABLE 1** GRADE profile: Bisphosphonate use in increasing BMD and decreasing reoccurrence of fractures in children with OI.

<table>
<thead>
<tr>
<th>Quality Assessment Criteria</th>
<th>Summary of Findings</th>
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<tr>
<td><strong>No. of Studies</strong></td>
<td><strong>Design</strong></td>
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<td><strong>Increasing bone mineral density</strong></td>
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| **Decreasing incidence of fractures** | 2 | 2 RCTs | No serious limitations | No serious indirectness | No serious imprecision | Serious inconsistencies | No bias likely | Bishop et al | 94 | 49 | 0.63 | 6 | NNT | Moderate | Critical |
| | | | | | | | Ward et al | 109 | 30 | 1.12 | 476 | NNT | |

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*a: In the Bishop et al study, groups differed in mean total body BMD at baseline. The treatment group had a baseline total body BMD Z score of -1.42 and -1.82 in the placebo group. Groups otherwise had a similar prognosis at baseline.*