Efficacy of Bisphosphonates in Increasing Bone Mineral Density and Decreasing the Incidence of Fractures in Children with Osteogenesis Imperfecta

Jami M.Y. Strapple
Pacific University

Follow this and additional works at: http://commons.pacificu.edu/pa

Recommended Citation
Efficacy of Bisphosphonates in Increasing Bone Mineral Density and Decreasing the Incidence of Fractures in Children with Osteogenesis Imperfecta

Abstract
Background: Osteogenesis Imperfecta (OI) is a rare, hereditary disorder that involves improper collagen synthesis, specifically, that of type 1 collagen, leading to bone fragility. There are four types of classification of OI, each varying in severity from multiple fractures to perinatal death. Bisphosphonates has recently been recognized as a pharmacologic treatment that aids in bone strength. More randomized controlled trials have been conducted to examine the efficacy of bisphosphonates in increasing the bone mineral density and decreasing the incidence of fractures in children with OI.

Methods: A comprehensive search of the medical literature was conducted using various search modalities including MEDLINE, CINAHL, AND ISI World of Science and using the keywords “osteogenesis imperfecta”, “children” and “bisphosphonates”. Specific examples of bisphosphonates were also used as keywords in the search such as [“pamidronate”OR “alendronate” OR “olendronate” OR risedronate]. Trials were only included if published in English after 2003 and if the trial was randomized and controlled. Bibliographic reference of prior systematic review was also examined to identify applicable literature. Studies were rated using the Jadad criteria.

Results: Nine articles were found that met the selection criteria, all of which were randomized controlled studies. Overall, it was found that in five studies the incidence of fractures was decreased in children with OI and in seven studies bone mineral density increased in children with OI.

Conclusion: Bisphosphonate therapy appears to increase bone mineral density and decrease the incidence of fractures in children with OI. However, results would be strengthened by a larger, longer, randomized controlled study. Many questions about the use of bisphosphonates in growing children remain including the long-term effects of bisphosphonates, optimal dosing, and more importantly the safety of bisphosphonates in children.

Degree Type
Capstone Project

Degree Name
Master of Science in Physician Assistant Studies

First Advisor
James Ferguson PA-C, MPH

Second Advisor
Annjanette Sommers MS, PAC

This capstone project is available at CommonKnowledge: http://commons.pacificu.edu/pa/195
Third Advisor
Rob Rosenow PharmD, OD

Keywords
Osteogenesis Imperfecta, bisphosphonates, children, pamidronate, alendronate, olendronate, risedronate

Subject Categories
Medicine and Health Sciences

Rights
Terms of use for work posted in CommonKnowledge.
Copyright and terms of use

If you have downloaded this document directly from the web or from CommonKnowledge, see the “Rights” section on the previous page for the terms of use.

If you have received this document through an interlibrary loan/document delivery service, the following terms of use apply:

Copyright in this work is held by the author(s). You may download or print any portion of this document for personal use only, or for any use that is allowed by fair use (Title 17, §107 U.S.C.). Except for personal or fair use, you or your borrowing library may not reproduce, remix, republish, post, transmit, or distribute this document, or any portion thereof, without the permission of the copyright owner. [Note: If this document is licensed under a Creative Commons license (see “Rights” on the previous page) which allows broader usage rights, your use is governed by the terms of that license.]

Inquiries regarding further use of these materials should be addressed to: CommonKnowledge Rights, Pacific University Library, 2043 College Way, Forest Grove, OR 97116, (503) 352-7209. Email inquiries may be directed to: copyright@pacificu.edu

This capstone project is available at CommonKnowledge: http://commons.pacificu.edu/pa/195
NOTICE TO READERS

This work is not a peer-reviewed publication. The Master’s Candidate author of this work has made every effort to provide accurate information and to rely on authoritative sources in the completion of this work. However, neither the author nor the faculty advisor(s) warrants the completeness, accuracy or usefulness of the information provided in this work. This work should not be considered authoritative or comprehensive in and of itself and the author and advisor(s) disclaim all responsibility for the results obtained from use of the information contained in this work. Knowledge and practice change constantly, and readers are advised to confirm the information found in this work with other more current and/or comprehensive sources.

The student author attests that this work is completely his/her original authorship and that no material in this work has been plagiarized, fabricated or incorrectly attributed.
Efficacy of Bisphosphonates in Increasing Bone Mineral Density and Decreasing the Incidence of Fractures in Children with Osteogenesis Imperfecta

Jami M.Y. Strapple

A Clinical Graduate Project Submitted to the Faculty of the School of Physician Assistant Studies Pacific University Hillsboro, OR For the Masters of Science Degree, August 14, 2010

Faculty Advisor: James Ferguson PA-C, MPH Clinical Graduate Project Coordinators: Annjanette Sommers MS, PAC & Rob Rosenow PharmD, OD
Biography

Jami Strapple is a native from Kailua, Hawai’i and graduated with a Bachelor of Science degree in Biology with an emphasis in Cellular and Molecular Biology from Pacific University of Oregon in 2003. After completion of her undergraduate studies, she returned home to Hawai’i and worked as a Physical Therapy Assistant before being accepted into Pacific University of Oregon’s Physician Assistant program in 2008. Jami will graduate as a PA in August of 2010, after which she will be moving back to Hawai’i. Jami looks forward to returning to Hawai’i to practice medicine, continue canoe paddling and spend time with her family.
Abstract

**Background:** Osteogenesis Imperfecta (OI) is a rare, hereditary disorder that involves improper collagen synthesis, specifically, that of type 1 collagen, leading to bone fragility. There are four types of classification of OI, each varying in severity from multiple fractures to perinatal death. Bisphosphonates has recently been recognized as a pharmacologic treatment that aids in bone strength. More randomized controlled trials have been conducted to examine the efficacy of bisphosphonates in increasing the bone mineral density and decreasing the incidence of fractures in children with OI.

**Methods:** A comprehensive search of the medical literature was conducted using various search modalities including MEDLINE, CINAHL, AND ISI World of Science and using the keywords “osteogenesis imperfecta”, “children” and “bisphosphonates”. Specific examples of bisphosphonates were also used as keywords in the search such as [“pamidronate”OR “alendronate” OR “olendronate” OR risedronate]. Trials were only included if published in English after 2003 and if the trial was randomized and controlled. Bibliographic reference of prior systematic review was also examined to identify applicable literature. Studies were rated using the Jadad criteria.

**Results:** Nine articles were found that met the selection criteria, all of which were randomized controlled studies. Overall, it was found that in five studies the incidence of fractures was decreased in children with OI and in seven studies bone mineral density increased in children with OI.

**Conclusion:** Bisphosphonate therapy appears to increase bone mineral density and decrease the incidence of fractures in children with OI. However, results would be strengthened by a larger, longer, randomized controlled study. Many questions about the use of bisphosphonates in growing children remain including the long-term effects of bisphosphonates, optimal dosing, and more importantly the safety of bisphosphonates in children.

**Keywords:** Osteogenesis Imperfecta, bisphosphonates, children, pamidronate, alendronate, olendronate, risedronate.
Acknowledgements

To my dearest family: Thank you for every word of encouragement and prayer for perseverance. I can’t imagine being part of a more supportive and loving family.

To Kamaka: Thank you for believing in me and encouraging me to reach my goals.
# Table of Contents

- Biography .................................................................................................................. 2
- Abstract ....................................................................................................................... 3
- Acknowledgements ...................................................................................................... 4
- Table of Contents ........................................................................................................ 5
- List of Tables ............................................................................................................... 6
- List of Abbreviations ................................................................................................... 6
- List of Appendices ....................................................................................................... 6
- Background .................................................................................................................. 7
- Methods ....................................................................................................................... 9
- Results ......................................................................................................................... 10
- Discussion .................................................................................................................... 17
- Conclusion ................................................................................................................... 22
- References ................................................................................................................... 24
- Tables .......................................................................................................................... 27
- Appendix ..................................................................................................................... 29
List of Tables

Table 1: Expanded Silience Classification of Osteogenesis Imperfecta
Table 2: Summary of Reviewed Literature

List of Abbreviations

OI…………………………………………………………………Osteogenesis Imperfecta
BMD………………………………………………………………...Bone Mineral Density
IV……………………………………………………………………………Intravenously
DXA………………………………………………………………………Dual energy X-ray absorptiometry

List of Appendices

Appendix A………………………………………………………..Description of Jadad Score Criteria
Efficacy of Bisphosphonates in Increasing Bone Mineral Density and Decreasing the Incidence of Fractures in Children with Osteogenesis Imperfecta

BACKGROUND

Osteogenesis imperfecta (OI) also known as “brittle bone disease” is a rare, hereditary disorder involving improper collagen synthesis, specifically type 1 collagen.\(^1\) This particular type of collagen is found in bone, ligaments, tendons, skin, sclera and dentin. Osteogenesis imperfecta is characterized by an array of clinical manifestations including osteoporosis with fractures, joint laxity, grey-blue sclera and dentinogenesis imperfecta.\(^2\) About 80-90% of the patients with OI have mutations in one of the two genes that encode for collagen type 1, COL1A1 and COL1A2 which are transmitted as autosomal dominant traits.\(^3,\,4\) Historically, OI has been classified into four clinical types by Sillence et al.\(^5\) (see Table 1), although through recent data by Glorieux et al.\(^6,\,7\) three additional types have been included which are not associated with collagen type 1 mutations. According to Sillence et al\(^5\), type I is the most common autosomal dominant, non-deforming characterized by short stature, triangular faces, joint laxity and blue-grey sclera and does not have dentinogenesis imperfecta. Type II is perinatally lethal affecting babies while \textit{in utero} or during the following months. Type III is moderately deforming, white sclera, short stature, severe scoliosis and dentinogenesis imperfecta. Lastly, type IV is similar to type I but with more severe deformity, white sclera and dentinogenesis imperfecta. The additional three types are not associated with blue sclera or dentinogenesis imperfecta. Clearly, OI presents in the young and must be treated
immediately to prevent serious outcomes associated with this disorder especially, bone fragility.

Historically, treatment of OI has focused on orthopedic care including, casting, splinting and rodding. In addition to orthopedic care, there have been various pharmacologic treatments that have not been found to be effective, including anabolic steroids, calcium, fluoride, magnesium, arsenic, diluted hydrochloric acid and growth hormones.\textsuperscript{2, 8, 9} It was not until 1987, that Devogelaer et al\textsuperscript{10} reported the first use of bisphosphonates in treatment for children with OI. His study explored the use of bisphosphonate in treatment in other bone conditions such as juvenile osteoporosis and Paget’s disease of bone. Bisphosphonates share a similar structure to pyrophosphate, a naturally occurring substance known to inhibit bone metabolism. Over time, bisphosphonates have evolved beginning with the first generation (e.g. etifronate), to second and third generation compounds, such as alendronate, pamidronate, risedronate and neridronate. The antiresorptive properties increase approximately ten-fold between generations. Newer bisphosphonates, such olpadronate, are even more potent.\textsuperscript{11} According to Rogers, bisphosphonates act on osteoclasts, disrupting the pathway and inducing death of these cells.\textsuperscript{12} It is important to note that children with OI have an abnormal collagen synthesis, creating bone fragility, thus bone is further reduced by osteoclastic activity. In addition, osteoblasts cannot keep up at the rate that osteoclastic activity is occurring, thus leading to low bone mineral density (BMD) and increased fractures secondary to bone fragility.\textsuperscript{12} Devogelaer\textsuperscript{10} in 1987 and Huaux et al\textsuperscript{13} in 1988, were the first to report a decrease in fracture rate and pain, with the use of bisphosphonates in children with severe OI. Then in 1997, Bembi et al\textsuperscript{14} first reported an
increase with BMD in children treated with bisphosphonates for period of 22 months to 29 months. The aims of treatment with bisphosphonates in children with OI are to increase bone strength and decrease the number of fractures occurring.

The goal of this systematic review is to examine the available medical research published to determine the efficacy of various types of bisphosphonates in increasing BMD and decreasing the incidence of fractures in children with OI.

**METHODS**

A comprehensive search of the medical literature was conducted using various search modalities including MEDLINE, CINAHL and ISI World of Science and using the keywords “osteogenesis imperfecta”, “children” and “bisphosphonates”. Specific examples of bisphosphonates were also used as keywords in the search such as [“pamidronate”OR “alendronate” OR “olendronate” OR “risedronate”]. Inclusion criteria for this systematic review were all in English language, randomized controlled trials published after 2003 which included children with OI and the use of bisphosphonates for decreasing incidence of fractures and increasing BMD. The included studies followed children with different types of OI, using various bisphosphonate therapies, mainly for looking at the incidence of fractures and increase in BMD. Excluded were cohort, both prospective and retrospective studies and case reports. After inclusion and exclusion criteria, nine studies were rated and assessed for quality using the Jadad criteria (see Appendix A).

After a preliminary search, a 2008 systematic review was located. The author’s literature search reviewed seven randomized controlled trials and one prospective cohort
study up to April 2007. A bibliography search was done for the seven randomized controlled trials that were reviewed in the 2008 systematic review which met all of the inclusion and exclusion criteria. An additional two randomized controlled trials, that were not included in the 2008 systematic review, met all of the inclusion and exclusion criteria and was examined.

RESULTS

A total of nine articles which met the inclusion and exclusion criteria were examined in this review (See Table 2). The average sample size was approximately 28.3, with the largest group studied consisting of 64 children with OI, and the smallest group consisting of 10. The shortest study lasted 18 months and the longest study lasted three years. All studies included in this review were randomized, controlled studies. Three trials were double-blinded, and in six, neither participants nor observers were blinded. All studies looked at children with OI treated with a bisphosphonate either orally or intravenously (IV).

Each study looked specifically at children with either one type of OI or various types of OI. Five studies included children with OI type I, III, and IV, two studies specifically included children with OI type I, one study included neonates with just OI type III and, lastly, one study included children with OI type III and IV. Eight trials excluded children with OI who had previously received bisphosphonate therapy.

Three studies examined intravenous bisphosphonate in children with OI. Antoiazzi et al examined infants with severe OI type III, 18-44 days old, for 18 months. This study design was a prospective, randomized, controlled study. This was not a double
blinded study and the method of randomization was not stated. The neonates were determined to have OI type III by clinical and radiographic evaluation. The aim of this study was to determine the efficacy of bisphosphonate therapy in the neonatal period in hopes to determine an appropriate age to start bisphosphonate therapy. Therapy consisted of neridronate 2mg/kg/body weight administered intravenously for two consecutive days, at three month intervals. Assigned were three groups: Group A started treatment after diagnosis, mean age 37 days, group B started treatment after six months, mean age 220 days and group C a historical control group. Vitamin D and calcium were maintained through diet or supplementation. Every three months, the number of fractures was measured and the fracture incidence was assessed by parental recall and diary confirmed by radiography, however, dual energy X-ray absorptiometry (DXA) measurements were not obtained due to young children being casted or unable to sit still. Results demonstrated a statistically significant decrease in number of fractures (p<0.05) in Group A compared to Group B and C during the first six months of treatment. In the second six months, groups A and B had a significant decrease in the number of fractures (p<0.05) compared to group C.15

Gatti et al16 also examined intravenous bisphosphonates in children with OI. This study examined prepubertal children with OI types I, III and IV, ages 6-11 for boys and ages 6-9 for girls, over three years. The Italian Patients’ Society (IPS) sent children from their society affected by OI. The study relied on the original diagnosis by the IPS. This study design was a randomized, controlled study. It was not blinded and the method of randomization was not stated in the study. The goal of this study was to demonstrate the efficacy of IV neridronate in children with OI. Therapy consisted of IV neridronate 2
mg/kg/body weight infused for 30 minutes every three months or no treatment, the ratio of the treatment group to control group was 2:1. Calcium and vitamin D levels were maintained through diet or supplementation. Radiographs at suspected sites of fractures were taken at baseline, 12 months and 36 months and DXA measurements were taken every six months. Results demonstrated several differences in characteristics between the two groups; however, they were not statistically significant. There was a statistically significant increase in spine and hip BMD in the treatment group (p<0.001) compared to the control group in the first year. During the following two years, there was an increase of 10-25% in BMD in the treatment group. During the first year of treatment, 45% of patients in the control group and 25% of patient in the treatment group had a non vertebral fracture, however this was not found to be statistically significant due to sample size. Furthermore, there was a significant decrease in relative risk reduction of fractures in the treatment group (RR=0.36; 95% CI, 0.15-0.87; p<0.05) compared to the control group, during the first year.16

Letocha et al17 studied 18 children with OI type III and IV, ages 4-13, for one year with an additional 6-21 months extended treatment period. This study design was a randomized, controlled, non-blinded study. The diagnosis of OI in the children was reviewed under an Institutional Review Board approved, protocol. Eight children included in the study were also co-enrolled in a recombinant growth hormone study. The aim of this study was to determine whether IV pamidronate would increase DXA spine measurements and improve functional ability. Therapy consisted of IV pamidronate 10mg/m²/day for three days every three months for one year or placebo. Four children included in the treatment group also received 0.06mg/kg/day for six days per week of
Humatrope. Children received calcium supplementation. Radiographs and DXA measurements were taken at baseline and every six months. After one year, it was determined by DXA z-scores that the treatment group had a significant increase in BMD compared to the control group, therefore, the treatment group continued for an additional 6-21 months. Results of this study demonstrated an increase in lumbar DXA z-scores (p<0.001) in the treatment group compared to the control group in the first year. Additionally, the lumbar DXA z-scores increased (p<0.005) over the second year in the treatment group. There was a decrease in the incidence of upper extremity fractures in the treatment group (p=0.05) compared to the control group in the first year. However, there was not a significant decrease in the incidence of fractures in the lower extremity in the treatment group.

There were four studies that examined oral bisphosphonates in children with OI. Bishop et al examined 53 children with moderate to severe OI type I, III and IV, for a length of two years. This study design was a randomized, double-blinded, dose-ranging study. The diagnosis of OI was based on phenotype with one or more of the following features including recurrent fractures affecting mobility or two or more crush fractured vertebrae causing deformity and requiring surgery. This study examined whether children with OI receiving the higher dose of risedronate weekly would have fewer fractures than the children with OI receiving the lowest dose of risedronate weekly. Therapy consisted of 0.2mg/kg/week, 1mg/kg/week, or 2mg/kg/week of risedronate for two years. Calcium supplementation was provided. The number of fractures were recorded and reported by families and confirmed by radiographs and DXA measurements were taken at each visit. The primary study outcomes measured were fracture incidence
and bone measurement outcomes. Results demonstrated that there was an overall decrease in the number of fractures during the study compared to two years prior to the study (p=.005) in all treatment groups. There was no significant decrease in incidence of fractures between the dosing groups. Dual energy x-ray absorptiometry values assessed in this study showed an increase in lumbar BMD (p=0.03) and total body BMD (p=0.0006) in the group receiving the highest dose of risedronate weekly. Overall, children with OI who received the highest dose of risedronate experienced an increase in lumbar and total body BMD.  

Rauch et al examined 26 children and adolescents with OI type I, 4-18 years old, for two years. This study design was a prospective, single-center, placebo-controlled, double-blinded- study. This study failed to mention method of randomization. The diagnosis of OI type I was made clinically. The study examined the safety and efficacy of oral risedronate in children with OI type I. Therapy consisted of either 15mg (<40kg) or 30mg (> 40 kg) once a week or placebo. Children were given calcium and vitamin D for supplementation. Radiographs and DXA measurements were obtained at baseline and at the end of study. The primary endpoint measured was change in lumbar spine BMD. Other endpoints were examined including radiographically confirmed fractures. Results of this study demonstrated an increase in lumbar spine BMD (p=0.003) in the treatment group when compared to the placebo group. There were no statistically significant changes in DXA measurements in hip, total body, radial metaphysis and radial diaphysis.  

Seikaly et al examined 20 children with OI types I, III and IV, 3-15 years old, for two years. This study design was a prospective double-blind crossover study. OI in
the children was diagnosed by the Silence criteria (see Table 1). The aim of this study was to determine if daily oral alendronate improves a child’s daily life. Primary endpoints included bone density measured by DXA. Secondary endpoints included rate of skeletal fractures. Therapy consisted of oral alendronate at a dose 5 or 10mg/d depending on weight. Patients who weighed less than 30 kg received 5 mg/d; patients who weighed more than 30 kg received 10mg/d. The control group received placebo. Children were maintained on alendronate for 12 months before crossing over to placebo for an additional 12 months and vice versa. Children received calcium and vitamin D supplementation. Dual energy x-ray absorbiometry and skeletal survey were obtained yearly. Results demonstrated a tendency to decrease the frequency of fractures however the effect was not statistically significant due to sample size. There was an increase in lumbar BMD (p<0.001) in the treatment group compared to the placebo group. There was no significant difference in order of administration of placebo versus alendronate in decreasing lumbar BMD (p=0.3623).20

Sakkers et al21 examined 34 children with OI types I, III and IV, ages 3-18, for two years. Children with OI were selected from a Children’s Hospital database in the Netherlands. This study only recruited children with restricted ambulation due to interests in functional mobility. The design was a randomized, double blinded, placebo-controlled study. The aim of this study was to determine if oral olpadronate has any effects on skeletal measurements and functional outcomes in children with OI. Primary endpoints were fracture incidence and skeletal densitometries. Therapy consisted of daily oral olpadronate 10mg/m² or placebo for two years. Calcium and vitamin D were given as supplementation. DXA and skeletal radiographs were obtained at baseline, one year and
end of study. Results of this study demonstrated an increase in spinal BMD (p=0.01) in the treatment group compared to the placebo group. Olpadronate was associated with a 31% reduction in relative risk of fractures long bone fractures (p=0.01) in the treatment group compared to the placebo group.\textsuperscript{21}

The remaining two studies examined intravenous bisphosphonate compared to an oral bisphosphonate in children with OI.\textsuperscript{22, 23} DiMeglio et al\textsuperscript{23} studied 18 children with OI type I, over the age of three, for two years. This study design was a prospective, partially randomized open label study. This study did not include a placebo-control. The diagnosis of OI was made by a multidisciplinary team including a geneticist, orthopedic surgeon and pediatric endocrinologist. This study examined whether or not there was a difference in oral alendronate versus IV pamidronate at increasing BMD. Therapy consisted of alendronate 1mg/kg/day orally in the form of tablets over four months and pamidronate disodium 1mg/kd/day intravenously for 3 consecutive days every four months for two years. Calcium was maintained through diet or supplementation. Every 4 months DXA was used to assess spine and total body BMD and radiographs assessed fracture history and current fractures annually. Primary endpoints measured were increase in BMD. Secondary endpoints, among others, were also examined including fracture incidence. Results demonstrated in this partially randomized study, that two children were assigned to intravenous therapy for abdominal pain accompanied by heme-positive stools and difficulty obtaining intravenous access before therapy. Results also reported that three children had hardware added and three different children had hardware removed during the study. Results of this study demonstrated that children had an increase in total body BMD (p<0.01) and lumbar BMD (p<0.01) for both combined oral
alendronate and IV pamidronate. There was an overall decrease in the fracture rate in the combined group (p<0.05). However, there is no significant difference between treatment groups.\(^{23}\)

DeMeglio et al\(^{22}\) studied 12 children with OI types I, III and IV, ages 3-18, for one year. The study design was an open-label, prospective, randomized clinical study. A clinical diagnosis of OI was made in the children. The aim of this study was to examine the efficacy of oral bisphosphonates in children with OI compared to IV. Therapy consisted of IV pamidronate 1mg/kg/d for three consecutive days every four months or daily oral alendronate 1mg/kg for four months. Daily calcium intake was supplemented. At every visit, DXA was obtained and fracture history was obtained by parental recall and by diary. Suspected fractures were confirmed by radiographs. Primary endpoints were changes in BMD. Secondary outcomes, among others, were fracture incidence. Results reported that two children broke randomization and were assigned to intravenous group because of chronic abdominal pain. Results demonstrated an increase in lumbar and total body BMD in both treatment groups (p<0.05). This study also demonstrated a decrease in number of fractures in all treatment groups over one year.\(^{22}\)

**DISCUSSION**

The characteristics of each study’s population varied slightly. All studies used children primarily 3-18 years old diagnosed with OI, with varying types of OI, except one study\(^{15}\) which looked primarily at neonates 18-44 days old with severe OI.\(^{15-23}\) Children were excluded in all studies if they had prior bisphosphonate therapy, except one study which did not mention whether or not they used that criteria in their selection of
Letocha et al\textsuperscript{17} included eight children with OI who were also co-enrolled in another protocol treatment on recombinant growth hormone; however they found no statistically significant difference in those children’s results.\textsuperscript{17} Five studies\textsuperscript{16, 18, 20, 21, 23} included children with OI type I, III, and IV, two studies\textsuperscript{19, 23} included children with mild OI type I and two studies\textsuperscript{15, 17} included children specifically with severe OI type III and IV. Overall, there still seems to be a limited amount of data specifically looking at milder forms of OI and other types of OI not associated with collagen type 1 mutations and children younger than three. Since, the clinical question is looking at specific outcomes, the primary and secondary endpoints examined in this review were specific to fracture incidence and BMD.

Many of the studies used various bisphosphonates as treatment in children with OI. It seemed that many of the studies included in this review assumed that these drugs work efficaciously in the treatment of children with OI and has forged without considering the basic questions “does one work better than another”, “what dosage is most effective or what route of administration is most effective”.

In each study, the route of administration of bisphosphonate differed. Many of the studies either looked at an oral or IV administration of a bisphosphonate compared to placebo\textsuperscript{15-17, 19-21} except one study\textsuperscript{18} which looked at three different doses to see if one particular dose had more of an effect than the other doses. Two studies\textsuperscript{22, 23} compared an IV administered bisphosphonate to an orally administered bisphosphonate. Both oral and IV bisphosphonates have demonstrated to be equally safe in children with OI.\textsuperscript{22, 23} However, oral administration of bisphosphonates has clear advantages over IV administration of bisphosphonates. Clearly, IV administration requires hospitalization.
which is expensive, time consuming and requires IV access. It also disrupts schooling and requires parents to take time off work. However, in children with functional immobility, fractures and intolerability with oral medications, IV administration would be beneficial option.

The dosing of bisphosphonates in each study was comparable when either administered orally or intravenously. Bishop et al\textsuperscript{18} demonstrated that children receiving the highest dose of bishphosphonate of 2mg/kg/week experienced an increase in BMD compared to the other treatment groups. There remain the questions as to optimal dosing of bisphosphonates and duration of treatment of children with OI.

Each study looked at many outcomes; however, only the relevant outcomes of incidence of fractures and BMD are addressed. A decrease in incidence of fractures was demonstrated in five studies.\textsuperscript{15-17,21,23} Increased bone mineral density was reported in seven studies.\textsuperscript{16-18,20-23} A statistically significant increase in lumbar BMD was reported in seven studies\textsuperscript{16-18,20-23}, a statistically significant increase in total body BMD was reported in three studies\textsuperscript{18,22,23} and a significant increase in hip BMD in one study.\textsuperscript{16} Overall, the efficacy of bisphosphonates in decreasing incidence of fractures and increasing bone mineral density is a promising.

**Limitations**

There were several limitations for this systematic review. The weakness of the studies included in this systematic review was the number of children evaluated in the studies. A disorder such as OI is so rare, that a significant result in a study with a treatment group of five seems hard to stand a chance of achieving meaningful
significance. The largest sample size in this study was 64 participants, thus the results are based on a limited study population. The validity of the results of the studies may have been easier to validate in a larger population, for example had the studies done a multicenter study since OI is rare, the results would have more validity. Many of the studies looked at children with various types of OI; however, there is limited data on other forms of OI which are not associated with collagen mutations.

Another limitation resulted from the fact that many of the studies were not blinded. Five studies were not blinded. By not blinding the participants, researches, parents, and clinical staff bias is introduced into the study. This is a limitation to the validity of the study. In addition, selection bias was demonstrated in two studies. Participants were randomized to groups but before treatment, were assigned to different groups that were randomized to, thus breaking randomization. These two studies professed to be randomized but broke randomization. Each study was assigned a Jadad score (see Appendix A). Three studies were randomized, controlled, double-blinded studies that received a Jadad score of 5. Two studies were randomized, controlled studies but not blinded, thus receiving a Jadad score of 3. Two studies received a Jadad score of 2. DiMeglio et al was not a blinded study and they verified that they broke randomization. Letocha et al was not a blinded study and failed to describe withdrawals and dropouts. Lastly, two studies were not double blinded and method of randomization was not mentioned and appropriate, thus they received a Jadad score of 1.

Four studies relied on parental recall for fracture history prior to treatment and during scheduled follow-up appointments that were confirmed by radiographs; however
this presents a possible recollection bias. Other studies, along with confirming any suspected fracture with a radiograph, had orthopedic assessments at baseline and follow-up to confirm fracture history that perhaps more reliable than personal recollections of parents. Researchers must place a reliance on data of the past that was recorded by parents. Thus, the results of the incidence of fractures must always be evaluated with some degree of skepticism.

**Confounders**

Confounding variables are another crucial part of every one of these studies. Some populations simply are not equal. As discussed earlier, children with OI have varying severities of their disease state. Two studies reported a significant decrease in incidence of fractures in children with severe OI compared another study that looked at children with mild OI, and that this difference could be responsible for a detection bias in that result in decrease in the incidence of fractures that have been noted in more severe types of OI compared to mild types of OI.\textsuperscript{15, 17}

DiMeglio et al reported three children had hardware removed and a different three children had hardware added which could potentially affect the results of BMD in that particular study.\textsuperscript{23} Once again, the reliance of the BMD results in those studies remains skeptical. If the study had dropped those participants and accounted for them in follow-up, the study might have more internal validity.
Further studies

Based on the results of the most current research presented here, additional study is clearly warranted. Future studies should follow the lead of the literature presented here with randomized, controlled, blinded studies, and should improve on their foundation by recruiting larger numbers of participants. They should do a better job of confirming the diagnosis of OI in their participants, making sure their participants do not have hardware implemented in them at the start of their study and making sure all participants are supplemented with calcium and vitamin D.

It would also be a good idea to consider comparing various bisphosphonates to see if one bisphosphonate is more efficacious than the others at improving BMD and decreasing incidence of fractures in children with OI. Also, future studies may examine the optimal dose of bisphosphonates in treating children with OI.

CONCLUSION

Based on the results of this literature review, evidence exists to support that bisphosphonates do in fact, decrease the incidence of fractures and increase BMD in children with OI. There are adequate amount of studies with internal validity that have demonstrated improvement in bone density with bisphosphonates. Many of the studies demonstrated a decrease in the number of fractures; however few studies have demonstrated statistically significance due to small sample sizes. Results would be strengthened by a larger, randomized controlled study. Many questions about the use of bisphosphonates in children with OI remain including research to assess the long-term effects of bisphosphonates in children with OI, optimal dosing as well as research on the
various types of OI not associated with mutations in collagen type 1 and more importantly, safety of bisphosphonates in children with OI.
REFERENCES


**TABLES**

Table 1: Expanded Sillence Classification of Osteogenesis Imperfecta

<table>
<thead>
<tr>
<th>Type</th>
<th>Clinical Severity</th>
<th>Typical features</th>
<th>Typically Associated Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Mild non-deforming</td>
<td>Normal height or mild stature; blue sclera; no dentinogenesis imperfecta</td>
<td>Premature stop codon in COL1A1</td>
</tr>
<tr>
<td>II</td>
<td>Prenatal lethal</td>
<td>Multiple rib and long-bone fractures at birth; pronounced deformities; broad long bones; low density of skull bones on radiographs; dark sclera</td>
<td>Glycine substitution in COL1A1 or COL1A2</td>
</tr>
<tr>
<td>III</td>
<td>Severely deforming</td>
<td>Very short; triangular face; severe scoliosis; grayish sclera; dentinogenesis imperfecta</td>
<td>Glycine substitutions in COL1A1 or COL1A2</td>
</tr>
<tr>
<td>IV</td>
<td>Moderately deforming</td>
<td>Moderately short; mild to moderate scoliosis; grayish or white sclera; dentinogenesis imperfecta</td>
<td>Glycine substitutions in COL1A1 or COL1A2</td>
</tr>
<tr>
<td>V</td>
<td>Moderately deforming</td>
<td>Mild to moderate short stature; dislocation of radial head; mineralized interosseous membrane; hyperplastic callus; white sclera; no dentinogenesis imperfecta</td>
<td>Unknown</td>
</tr>
<tr>
<td>VI</td>
<td>Moderately to severely deforming</td>
<td>Moderately short; scoliosis; accumulation of osteoid in bone tissue; fish scale pattern of bone of lamellation; white sclera; no dentinogenesis imperfecta</td>
<td>Unknown</td>
</tr>
<tr>
<td>VII</td>
<td>Moderately deforming</td>
<td>Mild short stature; short humeri and femora; coxa vara; white sclera; no dentinogenesis imperfecta</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

*Source:* 1
Table 2: Summary of Reviewed Literature

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients/ Population</th>
<th>Intervention/ length of study</th>
<th>Outcome(s)</th>
<th>Jadad Score/ Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bishop et al. (2010)</td>
<td>53 children, OI types I, III, and IV</td>
<td>0.2, 1, 2mg/kg/week of oral risedronate for 2 yrs.</td>
<td>Increase in lumbar and total body BMD with highest dose (2mg/kg/week); decrease in # of fractures in all treatment groups</td>
<td>5/5- No placebo, compared different doses of bisphosphonates.</td>
</tr>
<tr>
<td>Rauch et al. (2009)</td>
<td>26 children, OI type I</td>
<td>Daily oral risedronate 5 mg (&lt;40kg), 10mg (&gt;40kg) or placebo for 2 yrs.</td>
<td>Increase in lumbar BMD</td>
<td>3/5- Not a double blinded study.</td>
</tr>
<tr>
<td>DiMeglio, et al. (2006)</td>
<td>18 children, OI type I</td>
<td>Oral alendronate 1mg/kg/d for 4 mo.or IV pamidronate 1mg/kg/d for 3 consecutive days q 4 mo. for 2 yrs.</td>
<td>Increase in lumbar and total body BMD in treatment group; overall decrease in fracture rate in combined groups</td>
<td>2/5- Not a double blinded study, partially randomized- 2 children assigned to intravenous group</td>
</tr>
<tr>
<td>Antoniazzi et al. (2006)</td>
<td>10 neonates , OI type III</td>
<td>IV neridronate 2mg/kg for 2 days q 3 mo. or placebo for 18 mo.</td>
<td>Fracture incidence decreased when treatment was started immediately after diagnosis</td>
<td>1/5-Not a double blinded study, no method of randomization stated</td>
</tr>
<tr>
<td>DiMeglio et al. (2005)</td>
<td>12 children, OI with types I, III, and IV</td>
<td>IV pamidronate 1mg/kg/day 3 consecutive days q 4 months; Daily oral aledronate 1 mg/kg for 1 yr.</td>
<td>Increase in lumbar and total body BMD; demonstrated a decrease in fractures- not significant</td>
<td>3/5- Not a double blinded study</td>
</tr>
<tr>
<td>Seikaly et al. (2005)</td>
<td>20 children with types I, III, IV OI</td>
<td>Daily oral alendronate 5mg (&lt;30kg) or 10mg (&gt;43kg) or placebo for 2 yrs</td>
<td>Increase in lumbar BMD</td>
<td>5/5- Crossover study, double blinded study.</td>
</tr>
<tr>
<td>Gatti et al. (2005)</td>
<td>64 prepubertal children, OI type</td>
<td>IV Neridronate 2mg/kg infused for 30 min. q 3 mo or placebo for 3 yrs</td>
<td>Increase in lumbar and hip BMD; significant decrease in the number of fractures</td>
<td>1/5- Not a double-blinded study, no method for randomization stated</td>
</tr>
<tr>
<td>Letocha et al. (2005)</td>
<td>18 children, OI types III and IV</td>
<td>IV pamidronate 10mg/m²/day for 3 consecutive days q 3 mo. or placebo and 8 children on rGH received 0.06mg/kg /d for 6 days/week for 1 yr. and additional 6-21 mo. for treatment group</td>
<td>Increase in lumbar BMD, significant decrease in upper extremity fractures</td>
<td>2/5- Not a double blinded study, 8 children were given injection of growth hormone during course of the study</td>
</tr>
<tr>
<td>Sakkers et al. (2004)</td>
<td>34 children, OI type I</td>
<td>Daily oral olpardonate 10mg/m²/d or placebo for 2 yrs</td>
<td>Increase in lumbar BMD, significant decrease in long bone fractures</td>
<td>5/5- double blinded trial</td>
</tr>
</tbody>
</table>
APPENDIX

Appendix A
Description of Jadad Score Criteria

<table>
<thead>
<tr>
<th>Jadad Score Calculation</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was the study described as randomized (this includes words such as randomly, random, and randomization)?</td>
<td>0/1</td>
</tr>
<tr>
<td>Was the method used to generate the sequence of randomization described and appropriate (table of random numbers, computer-generated, etc)?</td>
<td>0/1</td>
</tr>
<tr>
<td>Was the study described as double blind?</td>
<td>0/1</td>
</tr>
<tr>
<td>Was the method of double blinding described and appropriate (identical placebo, active placebo, dummy, etc)?</td>
<td>0/1</td>
</tr>
<tr>
<td>Was there a description of withdrawals and dropouts?</td>
<td>0/1</td>
</tr>
<tr>
<td>Deduct one point if the method used to generate the sequence of randomization was described and it was inappropriate (patients were allocated alternately, or according to date of birth, hospital number, etc).</td>
<td>0/-1</td>
</tr>
<tr>
<td>Deduct one point if the study was described as double blind but the method of blinding was inappropriate (e.g., comparison of tablet vs. injection with no double dummy).</td>
<td>0/-1</td>
</tr>
</tbody>
</table>