Prevalence and Treatment of OI-Related Hearing Loss with Bisphosphonates

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Abstract

Background: Osteogenesis Imperfecta (OI) is a bone disorder most commonly resulting from a dominant mutation in type I procollagen genes. Clinical manifestations may include brittle bones, blue sclera, and hearing loss. The prevalence of hearing loss in OI varies from 50-92%. Bisphosphonates are used to treat the orthopedic symptoms of OI. However, recent research suggests bisphosphonates may halt the progression of OI-related hearing loss.

Methods: This is an IRB-approved retrospective review of 179 individuals with OI. 52 individuals were included due to availability of an audiogram. Statistical analysis consisted of t-test, bivariate correlation, and one-way ANOVA. Hearing tests were conducted at an ENT office or via a clinically-validated tablet audiometer at our institution.

Results: Most of the population were female (N = 39) with average age of 30.9 ± 19.3 years. 48% (25/52) of study participants did not display hearing loss, nine of whom had taken bisphosphonates. 52% (27/52) of individuals with audiograms displayed hearing loss, 13 had been treated with bisphosphonates for orthopedic symptoms. PTA correlated with age but not with duration of bisphosphonate treatment.

Conclusion: Our results suggest a diagnosis of any type of OI significantly increases the risk of hearing loss, beginning at a younger age than in the general population. The effects of bisphosphonates on ameliorating hearing loss are equivocal. Prospective, longitudinal studies are required to fully evaluate the efficacy of bisphosphonate treatment on hearing loss in this population. Poor compliance in following physician recommendations for audiological evaluation suggests further education within the OI population and those who care for them is warranted.

Keywords

Osteogenesis imperfecta, Skeletal dysplasia, Bisphosphonates, Hearing loss, Osteochondrodysplasia, Tablet audiometer

Abbreviations

OI: Osteogenesis Imperfecta; PTA: Pure Tone Average; LPTA: Left Pure Tone Average; RPTA: Right Pure Tone Average; LCRC: Linked Clinical Research Center

Introduction

The prevalence of hearing loss in Osteogenesis imperfecta (OI) varies from 50-92% [1]. OI-related hearing loss can be conductive, mixed, or sensorineural. These individuals may require amplification, stapes surgery, or cochlear implants. At the present time, the most effective treatment for hearing loss in OI is unknown; however, there may be a pharmacological treatment that could prevent or mitigate the intensity of hearing loss in this population.

Osteogenesis Imperfecta is a group of genetically heterogeneous connective tissue disorders that usually result from a dominant mutation in type I procollagen genes, COL1A1 and COL1A2, which alter either the quality or quantity of type I collagen [2]. Clinically, OI is grouped into several types, with type I being the mildest, type IV a moderate form of OI, and type III the most severe, survivable form of OI [2]. OI can also be classified by the gene the collagen mutation occurs in [3]. Type I OI most commonly demonstrates haploin-
sufficiency mutation of the COL1A1 gene, whereas the majority of individuals with types II, III and IV OI have a qualitative abnormality of type I collagen. Although clinical manifestations of OI vary by type, all forms are characterized by brittle bones with a predisposition to fracture. Short stature, blue sclerae, cardiopulmonary insufficiency, dental problems, and hearing loss may also be present. Hearing loss is most common in type I OI, usually becoming apparent between the ages of 20 and 30 years [3].

Common inner and middle ear problems in OI include microfractures of the otic capsule and middle ear ossicles, deficient ossification, and demineralization of the otic capsule [4]. One study reported that the success of stapedectomy, often successful in the general population, can be complicated by fixation and excessive thickness of the stapes footplates and ossicular fragility in individuals with OI [1]. In another study, however, with a larger number of procedures in OI, the results were similar to those seen with otosclerosis surgery, with a few minor exceptions explained by the disease process [5]. The same paper reported no ossicular fragility. Despite the characteristic demineralization of the cochlea in OI, cochlear implants can still greatly benefit this population [1].

As previously mentioned, there is the possibility of a pharmacological treatment for hearing loss in OI: Bisphosphonates. Bisphosphonates are a class of drugs used to prevent osteoclast resorption and osteoblast apoptosis, thus decreasing bone turnover and increasing bone mineral density over time [6,7]. Bisphosphonates have been used to increase bone density and cortical bone width and decrease cortical bone porosity in osteoporosis, Paget’s disease of bone, and OI [8]. Though bisphosphonates are FDA-approved for use in treatment of individuals with osteoporosis and Paget’s disease of bone, they are not approved for use in OI; however, bisphosphonates are widely considered standard-of-care treatment for children with OI [9,10]. Recent studies suggest that bisphosphonates prescribed for orthopedic symptoms may also improve hearing loss associated with some disorders such as OI and otosclerosis [11-13]. One study reported on oral Risedronate or intravenous Zoledronate treatment in 10 individuals with otosclerosis, which has clinical and histopathological otic capsule similarity to OI [11]. Hearing stabilized in 8 of the individuals, and 2 individuals had improved word recognition scores and/or bone conduction pure tone averages [11]. In addition, bisphosphonates (either pamidronate 1 mg/kg twice monthly or zoledronic acid 0.05 mg/kg four times monthly) were used to treat OI-related hearing loss in 36 children at the Royal Children’s Hospital in Melbourne. They reported no functionally significant hearing loss by the age of 20 years, in contrast to untreated historical controls who showed a 15-63% rate of functionally significant hearing loss by that age [12].

Objectives

The current study aims to build on this research and to better characterize the relationship between bisphosphonate use and progression of hearing loss in individuals with OI. This is especially important because individuals with type I OI, who are reported to have the highest risk for hearing loss, have the mildest orthopedic symptoms and are therefore rarely treated with bisphosphonates. If bisphosphonate use results in improved hearing, bisphosphonates could become a standard treatment for individuals with type I OI.

Methods

This is an Institutional Review Board-approved retrospective review of the medical records of 179 individuals with OI from a single institution (Hospital for Special Surgery, New York City, NY). Inclusion criteria were a clinical diagnosis of OI and availability of an audiogram. Audiograms were either conducted by an audiologist or via testing in our clinic using a tablet audiometer (SHOEBOX® Audiometry) [14,15]. Demographic data, including age, sex, OI type, genetic test results, and bisphosphonate history were collected. Audiogram measurements at 500, 1000, 2000, 3000, and 4000 Hz were used to calculate the right and left ear pure tone averages (RPTA and LPTA, respectively). Degree of hearing loss was categorized as normal, mild, moderate, moderately-severe, severe, or profound [16]. Clinically significant hearing loss was defined as pure tone thresholds > 25 dB. Independent and paired samples t-tests were utilized to assess variations between pure tone measurements in individuals treated and untreated with bisphosphonates. Bivariate analysis was completed for all continuous variables, and one-way ANOVA was utilized for all between group analyses. Results were considered significant if p < 0.05. All statistical analysis was conducted using SPSS 22 for Windows (IBM SPSS Statistics, NY, USA). All figures were generated with GraphPad Prism version 8.0.0 for Windows (GraphPad Software, CA, USA).

Results

Fifty-two individuals (29% of all charts reviewed; 104 ears) were included in the study, 50% of whom had hearing tested with an external provider, while the others were tested with the tablet audiometer. The cohort consisted of 39 females and 13 males, ranging from 2-73 years of age (average 30.9 ± 19.3 years). Twenty-three individuals had type I OI, 12 had type III OI, 15 had type IV OI, one had type V OI, and one had type VIII OI. Genotype was available for 34 individuals (62.9%). Breakdown of the study population by OI type and age are shown in Figure 1.

Twenty-two individuals (42%) had prior or ongoing bisphosphonate treatment, eight of whom were actively receiving bisphosphonate treatment at the
in six individuals (11.5%), three of whom had prior bisphosphonate treatment. Vertigo was present in three individuals (6%), all of whom had prior bisphosphonate treatment. Twenty-two individuals (81%) with hearing loss had a bilateral loss. Four individuals (8%) had stapedectomies in the past. Right ear pure tone thresholds did not significantly differ from left ear thresholds. There was no significant difference in hearing loss between males and females (Males: 38.5% HL; Females: 56.4% HL; p = 0.472) or between OI types (Figure 3). There were no clinically significant differences in hearing with prior or ongoing bisphosphonate use between all subgroups, and the only statistically significant difference was left ear PTA at 500 Hz was worse in those with prior or ongoing bisphosphonate treatment (p = 0.022). PTA significantly correlated with age (r = 0.419, p < 0.001; Figure 4), but not with duration of bisphosphonate treatment (r = 0.153, p = 0.124). Prevalence of hear-

![Figure 1](image1.png)

**Figure 1:** Study population age and diagnosis. The study population skews younger (30.08 ± 19.28 years), but there is an even distribution of type of OI by age decade.

![Figure 2](image2.png)

**Figure 2:** Hearing loss prevalence by bisphosphonate treatment status. There is no statistically significant difference in hearing loss by bisphosphonate treatment status.

time of hearing testing. Average duration of bisphosphonate treatment was 4.57 years (range 1 month-12 years). Twelve individuals had prior alendronate treatment, four had pamidronate, three had Zoledronate, one had Risedronate, and two individuals had previous unspecified bisphosphonate treatment. All individuals who were treated with bisphosphonates were given the drug to treat orthopedic, not audiological symptoms. Thirteen individuals with prior bisphosphonate treatment had at least mild hearing loss at one or more frequencies: 10/12 treated with Fosamax; 1/4 with Pamidronate; 1/3 with Zoledronate; 1/2 with an unspecified bisphosphonate treatment, and none of the individuals treated with Risedronate. Fourteen individuals with no prior bisphosphonate treatment had at least mild hearing loss. There was no significant difference in PTA between individuals with and without prior bisphosphonate treatment (Figure 2). Tinnitus was present...
and those who were not. With this finding, it is important to note that many of these individuals had not had baseline hearing testing until years after bisphosphonate treatment ended. Additionally, study participants were treated with different types of bisphosphonates, which could have varying effects on hearing loss.

Age significantly correlated with LPTA and RPTA, which follows patterns of hearing loss in the general population. However, our cohort skewed younger (30.08 ± 19.28 years) and had a greater prevalence of hearing loss than the 14% expected in the general population (ages 20-69 years) [17]. The study population also had a higher prevalence at a younger age, with 60% prevalence of loss for individuals in their 20s, 83% in their 30s, and 67% in their 40s. This suggests that OI significantly influences risk of hearing loss.

Discussion

Our results demonstrate a 52% (27/52) prevalence of hearing loss in audiograms in a sample of individuals with OI, which is consistent with the previous literature [1]. Contrary to recent reports in literature [11-13], hearing loss patterns in our study were similar between individuals previously treated with bisphosphonates and those who were not. With this finding, it is important to note that many of these individuals had not had baseline hearing testing until years after bisphosphonate treatment ended. Additionally, study participants were treated with different types of bisphosphonates, which could have varying effects on hearing loss.

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Though hearing loss is a significant issue in this population and may decrease quality-of-life, there was a lack of compliance in following physician recommendations for audiological evaluation. Only 29% of our population completed an audiogram. We identified twenty-one individuals who missed and did not reschedule audiology exams that were coordinated by our staff. Interestingly, two of those individuals reported experiencing progressive hearing loss. This compliance rate is consistent with what has been reported in larger longitudinal studies of OI. For example, the Linked Clinical Research Center’s (LCRC) multi-center study of individuals with OI recommended annual audiometry for all participants, but only 19% had one or more audiogram [18]. One potential explanation for this compliance rate is that individuals and families may not consider hearing problems to be an urgent medical problem, and perhaps prioritize treatment for other symptoms of OI. Another possibility is that individuals with OI do not perceive that hearing loss impacts their activities of daily living. Seventeen percent (5/29) of LCRC participants with documented hearing loss by audiometry did not perceive they had hearing loss, further demonstrating the importance of incorporating audiological testing into standard treatment protocol for OI. It is important to note that hearing loss is not only an issue of quality-of-life, but also one of safety. Hearing loss may impact the ability of individuals who are wheelchair bound or who ambulate with assistance to safely and independently navigate in the community. Further research is necessary to explore motivations and possible barriers to seek audiometry in this population.

Furthermore, our analysis suggests that greater communication and education of the prevalence of hearing loss in this patient population between those who care for this population is warranted. We identified eleven additional individuals that were seen by an otolaryngologist but did not have their hearing tested. Seven of these eleven individuals were receiving bisphosphonate treatment and did not have prior audiograms. Regular and consistent hearing testing in adults with OI is necessary beginning in adolescence (second decade), as our data shows the risk of hearing loss dramatically increases from this point onwards. If hearing loss is suspected or perceived at any point, testing should be conducted promptly, regardless of age. Detection of hearing loss through routine hearing testing would allow for early intervention with bisphosphonate treatment, which could slow or prevent the progression of hearing loss. Not only was the overall prevalence of hearing loss in this population three times greater than the general population, but the prevalence of hearing loss in individuals in their 20s and 30s was also significantly greater than what is reported in the general population [17,19]. Therefore, it is imperative that hearing tests are conducted routinely in individuals with OI beginning in adolescence. Hearing testing should not be limited only to individuals with type I OI, but should include individuals with all types of OI. Prior studies have demonstrated that hearing loss is great-

![Figure 5: Prevalence of hearing loss in the study population. There is a much higher prevalence of hearing loss in the OI population compared to the general population, beginning at a younger age.](image-url)
est in the mildest form of OI [1]. This does not hold true in our study, as the prevalence of hearing loss was found to be approximately equal among individuals with Types I, III, and IV.

Limitations

The limitations of this study include the small sample size, retrospective nature of analysis, and lack of longitudinal data, which may limit the generalizability of these findings. Females were also overrepresented in this sample, comprising 75% of our cohort. Family history of hearing loss was not available for all cases, limiting the ability to separate familial and age-related hearing loss from OI-related hearing loss. For the 50% of the study population with professional audiometry testing, there was variability in audiogram providers, and no mechanism to assess inter-rater reliability. Although all individuals with OI were referred for annual audiometry, it is possible that the 50% of the cohort who pursued the recommended professional testing represents a more conscientious group, or may have experienced hearing loss significant enough to interfere with their activities of daily living, creating a potential source of bias in this study.

Conclusion

Given the high prevalence of hearing loss across all types of OI, more studies are needed to elucidate an effective treatment in this population. Bisphosphonates may have the potential to halt or slow OI-related hearing loss in adults, and prevent hearing loss in children and adolescents. Unlike other treatments that are adapted from the non-OI population [1], bisphosphonates target the specific, bony etiology of hearing loss in OI, treating the source, rather than the generalized symptoms, of inner ear abnormalities. Only 36.3% of the individuals with audiograms who were treated with bisphosphonates in this study had type I OI. If future research confirms that bisphosphonates ameliorate OI-related hearing loss, this medication could become standard of care in people with type I OI, who may not otherwise be indicated for bisphosphonate treatment of orthopedic symptoms.

This report contributes to the sparse literature on the use of bisphosphonates for treatment of hearing loss in OI. Future studies should collect prospective, longitudinal data from a broader sample of individuals with OI.

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Author Contributions

All Authors are equally contributed for 1) Substantial contributions to conception or design of the work, or the acquisition, analysis or interpretation of data; 2) Drafting the article or revising it critically for important intellectual content; 3) Final approval of the version to be published; 4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Compliance with Ethical Standards

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All work was performed at Hospital for Special Surgery, NY, NY. This study was performed in accordance with the ethical standards in the 1964 Declaration of Helsinki and regulations of HIPPA. Details that might disclose the identity of the subjects under study were omitted. IRB approval was obtained at Hospital for Special Surgery for this study.

References


