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REVIEW

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Bisphosphonate therapy in otosclerosis: A scoping review

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Abstract

Objective: Otosclerosis, a leading cause of deafness in adults, results from defective bone remodeling of the otic capsule. Bisphosphonates have been used to decrease bone remolding in many diseases, including otosclerosis. This study analyzes whether current literature supports bisphosphonate therapy as an effective treatment for otosclerosis.

Design: Scoping review.

Methods: A search was performed in three electronic databases; PubMed, Scopus, and Cochrane Control Trials. Articles were screened independently by two masked reviewers based on prespecified inclusion and exclusion criteria. After unmasking, the two reviewers resolved discrepancies through discussion.

Results: From the search, 35 unique articles were identified for analysis. The dates of these publications range from 1982 to 2018. Further title and full-text review identified six articles for inclusion in this review. Three of the studies included are randomized controlled trials (RCT)s, and three are retrospective case reviews. These studies analyzed bisphosphonate therapy regimens, but dose and study length varied, making direct comparisons difficult. Only one RCT study was able to show a statistically significant change between patients treated with bisphosphonates compared to a control group.

Conclusions: The efficacy of bisphosphonates for halting bone remodeling in otosclerosis remains unclear. Reviewing the literature, we found significant variations in experimental design and few studies of high-level evidence. Future RCTs investigating therapies for otosclerosis are needed before a firm conclusion about bisphosphonates efficacy as a pharmacological treatment of otosclerosis.

Level of Evidence: 3a.

KEYWORDS

bisphosphonates, hearing loss, Otosclerosis, otospongiosis, scoping review

1 | INTRODUCTION

The otic capsule is extremely dense bone that normally experiences no remodeling in adults as development of the otic capsule finishes around 26 weeks gestation.[1] Otosclerosis (also called otospongiosis) is a disease of defective bone remodeling of the otic capsule characterized by resorption and subsequent disorganized bone regrowth.[2] The presence of histologic osteosclerotic foci in Caucasians is

estimated to be 3.4%,[3] yet only 0.3% of the population develops clinical otosclerosis. For many, this disease confers no symptoms. In some patients, the stapediovestibular joint undergoes bone remodeling such that the stapes footplate will be fixed within the oval window, preventing free vibration of the stapes within the oval window (Figure 1), gradually progressing to a conductive hearing loss as the lesion extends. For some patients, cochlear otosclerosis may contribute to the development of sensorineural hearing loss (SNHL).[4] An estimated 34% of patients with otosclerosis develop significant sensorineural hearing loss.[5]

Currently, stapedotomy or stapedectomy is the main treatment option for patients with otosclerosis. These surgical procedures remove portions of the stapes footplate to insert a prosthetic that is anchored to the lenticular process of the incus bone. This surgical procedure is highly effective at restoring the conductive component of hearing loss; however, it has no effect on sensorineural hearing loss. A pharmacological treatment would aim to slow or even halt the progression of the disease.[6] While sodium fluoride was initially used as therapy for treating otosclerosis; there is limited evidence of efficacy from controlled trials and systematic reviews.[7] Bisphosphonates have replaced sodium fluoride as treatment in other metabolic bone disorders such as osteoporosis and Paget disease.[8] Bisphosphonates are being considered for use in the treatment of otosclerosis and have been shown to potentially stabilize progression of SNHL.[9] This is a scoping review of current literature on the use of bisphosphonate treatment for stabilizing otosclerosis.

2 | METHODS

This scoping review of bisphosphonate treatment on otosclerosis was granted IRB exemption from the University of Texas Medical Branch. In June 2020, the research librarian at the University of Texas Medical Branch performed a database search in Scopus, Ovid, MEDLINE, and Cochrane Library. The search terms included "otosclerosis" (otospongiosis), "bisphosphonates," and other relevant synonyms (Table 1). No limits were set on the search. The database search results were collected, and duplicate articles were removed.

Article titles and abstracts were then reviewed by two authors (R. E. Z. and B. J. M.) using the systematic reviews web application Rayyan QCRI. In this software, these two authors were blinded and independently reviewed the articles for relevance within prespecified inclusion and exclusion criteria. Inclusion criteria included publications with original data reporting on the effect of any bisphosphonate medication in the management of otosclerosis with appropriate study design. Exclusion criteria included non-English language articles, background articles, case studies with less than or equal to four subjects, case reports, cadaveric studies, and animal studies. The authors then compared their reviews, and disagreements about study inclusion were resolved with discussion. The remaining articles underwent full-text review by four authors (R. E. Z., R. E. A., Z. K. W., and B. J. M.).

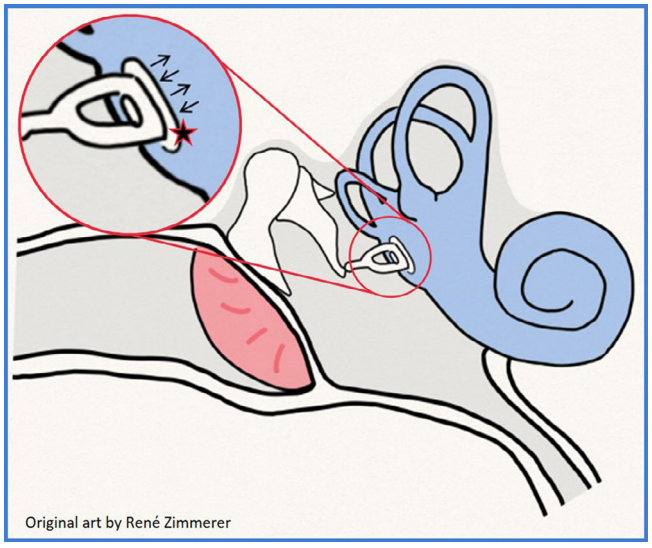

FIGURE 1 Middle ear anatomy

3 | RESULTS

A total of 62 articles were identified, 27 of which were duplicates and subsequently removed. After screening the 35 articles based on title and abstract, 29 articles were excluded based upon exclusion criteria (Figure 2). Six articles were included in this scoping review. The papers identified are listed in Table 2, which summarizes the data and key findings. Three articles were randomized controlled trials (RCTs) (level

TABLE 1 Search syntax

(otoscleros* OR otospongios* OR exp otosclerosis) AND (exp diphosphonates/OR bisphosphonate* OR diphosphonate* OR alendronate OR exp alendronate/OR Fosamax OR MK-217 OR MK217 OR clodronic acid/clodronic acid* OR dichloromethylenebisphosphonate* OR dichloromethylene bisphosphonate* OR Cl2MDP OR dichloromethanedisphosphonate OR exp etidronic acid/OR etidronic acid* OR hydroxyethylidene disphosphonic acid OR etridonate OR hydroxyethanediphosphonate OR ethanhydroxyphosphate OR ethanhydroxydiphosphonate OR HEDSPA OR Xidifon OR Xydiphone OR Xidiphon OR Didronel OR ibandronic acid OR exp ibandronic acid/OR ibandronate OR Boniva OR Bonviva OR RPR 102289A OR RPR102289A OR Bondronat OR "BM 21.0955" OR BM 210955 OR BM210955 OR exp pamidronate/OR pamidronate* OR AHPrBP OR aminopropanehydroxydiphosphonate OR amidronate OR aminohhydroxypropylidene diphosphate OR pamidronic acid* or Aredia OR exp risedronic acid/OR risedronic acid* OR Altevia OR risedronate sodium OR Actonel OR risedronate OR exp technectium Tc 99M medronate/OR technetium Tc 99m medronate* OR Tc-99 medronate or technetium methylene diphosphonate OR technetium Tc 99m methylenediphosphonate or 99mTc methylene diphosphonate OR 99mTc-MDP OR Tc-99m MDP OR exp disphosphonates/OR zoledronic acid OR exp zoledronic acid/OR zoledronic acid* OR CGP 42446A OR CGP42446A OR CGP-42446 OR CGP42446 or Zometa OR zoledronic acid anhydrous OR zoledronate)

Note: Search Syntax for the databases: MEDLINE, Scopus, Cochrane Clinical Trials; Field of search was the article titles and abstracts.

1 evidence), and three were retrospective case reviews (level 4 evidence).

Table 2 provides an overview of the characteristics of the six studies and shows they all differ in the duration of treatment, number of subjects, and bisphosphonate dosage. All studies, except two published by de Oliveira Vicente et al.[12,13] evaluated subjects with SNHL. The de Oliveira Vicente group stated most subjects presented with SNHL and that all subjects lacked a history of surgery in the examined ear. The clinical outcomes also varied with each study.

The Kennedy et al. study evaluated air conduction thresholds, bone conduction thresholds, and speech discrimination.[10] The de Oliveira Vicente et al. study evaluated air conduction thresholds, bone conduction thresholds, speech discrimination, and speech recognition thresholds.[12] Both the Quesnel et al. and Jan et al. studies reported bone conduction thresholds and speech discrimination.[9,14] The Brookler and Tanyeri group evaluated hearing using a self-evaluation questionnaire.[11] Brookler and Tanyeri also compared hearing tests of 103 subjects but did not specify which aspect of the hearing test or tests were used to quantify changes (pure tones, speech recognition threshold, or speech discrimination). Though diagnostic studies were excluded in this review, one study, de Oliveira Vicente et al.,[13] used MRI signal intensity differences before and after treatment in a subjective manner (using human interpretation) and an objective manner (using computer software) as outcome measures to evaluate disease progression.

The bisphosphonate generation also varied among the studies. Later generation bisphosphonates such as alendronate, risedronate, and zoledronate were used in four studies. Etidronate, a first-generation bisphosphonate, was used in two studies which use air and bone conduction threshold (Kennedy et al.[10]) and a questionnaire (Brookler and Tanyeri)[11] as outcome measures. The Brookler and Tanyeri study was a retrospective case review of the efficacy of etidronate in treating neurological symptoms associated with otosclerosis (dizziness, SNHL, tinnitus, and Meniere's syndrome) in patients whose previous sodium fluoride treatment appeared ineffective.[11] While the study included 896 patients in total, only 265 patients had SNHL. This was the largest number of subjects in a single study. The dose and treatment length varied for each patient depending on the severity and progression of their hearing loss. This study used a questionnaire to quantify changes in hearing loss as well as comparing hearing results for 103 patients who had hearing results available for comparison. Of these 103 patients, comparison to previous hearing tests showed 71% had no change, 21% showed improvement, and 2% showed worse hearing after approximately 6 months of etidronate therapy. This preliminary study suggested bisphosphonate therapy appeared to be a more effective treatment for neurological symptoms than sodium fluoride.

Of the six articles, there were two pairs of studies using the same populations. It is important to note these two pairs of studies are closely related to each other. There is a potential to overrepresent the findings of these studies as two subject populations represent four of the six studies in this review.

One pair of linked studies includes the study from Jan et al.,[14] which is a long-term follow-up of Quesnel et al.'s[9] original research focusing on the stabilization of bone conduction PTA and word recognition scores (WRSs) in patients with SNHL and surgically confirmed otosclerosis. Jan and colleagues'[14] lost three patients to follow-up and therefore evaluated only 14 of the original 19 ears from the original study. Both the original 2012 and follow-up 2017 studies found no significant change in either the BC-PT or the WRSs when comparing the immediate pretreatment data to the 1-year post-treatment data. These were the only studies that published audiological data during the 1-year time interval before the study began. Audiologic data for WRS and bone conduction threshold PTA for the first available and 1-year pretreatment time intervals were reported for six patients (12 ears) in the Quesnel et al.[9] study. This allows quantification of the

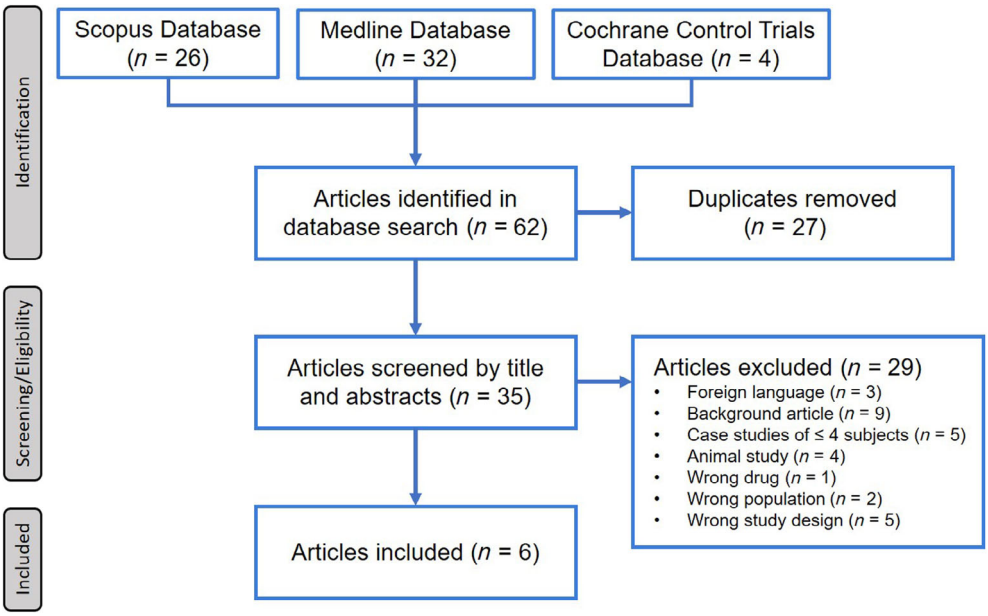

FIGURE 2 PRISMA diagram

TABLE 2 Summary of articles

Author (year)	Study design	Number of subjects	Treatment	Duration of treatment	Last follow up	Main outcome measures	Results
Kennedy et al. (1993)[10]	Double-blind RCT	26 subjects	• Control: 12 subjects[a,b] • Etidronate (20 mg/kg/day): 14 subjects[c,b] Cycles of pulsed doses[d]	2 years	2 years	1. Air conduction threshold (1000, 2000, and 4000 Hz) 2. Bone conduction threshold (500, 1000, and 2000 Hz) 3. Average discrimination scores	1. No statistically significant difference between groups. 2. Insufficient data for statistical analysis. 3. No statistically significant difference between groups.
Brookler et al. (1997)[11]	Retrospective case review	265 patients for SNHL[e]	• Etidronate (400 mg/day) Pulsed dosing adjusted based on improvement or worsening of symptoms	Varied based on symptoms	Ranged from 6 to 57 months	1. Comparing hearing tests (103 patients)[f] 2. Patient self-evaluation of hearing loss	1. Of 103 patients, hearing[f]: a. Remained the same (73 patients). b. Improved (28 patients). c. Declined (2 patients). 2. 162 patients self-reported: a. No improvement (44 patients). b. Improved (114 patients). c. Improved to normal hearing (4 patients).
Quesnel et al. (2012)[9]	Retrospective case review	10 patients (19 ears)	• 5 mg Zoledronate (parenteral) • 35 mg Risedronate (oral)[g]	• Zoledronate: single infusion • Risedronate: weekly[h]	Ranged from 8.8 to 18.8 months	1. Bone conduction pure tone threshold averages (PTA) (500, 1000, 2000, and 4000 Hz) 2. Word recognition scores (WRS)	1. No significant change measured in either BC-PTA[i] or WRS[j] for patient's pre- and post-treatment. 2. No statistically significant change in either BC-PTA[i] or WRS[j] for patients before and after stapedectomy.
de Oliveira Vicente et al. (2012)[12]	Double-blind RCT	26 patients (42 ears)[k]	• Control: 15 ears • Alendronate (10 mg/day): 11 ears • Sodium fluoride (20 mg/day): 16 ears	6 months	After completing treatment[l]	1. Air and bone conduction thresholds (500, 1000, 2000, and 4000 Hz) 2. Air bone gap 3. Speech recognition threshold (SRT) 4. Speech discrimination (PB)	1. No statistically significant difference was found in air-bone gap, speech recognition threshold, and speech discrimination when comparing the pre- and post-treatment values.
de Oliveira Vicente et al. (2015)[13]	Double-blind RCT	26 patients (42 ears)[k]	• Control: 15 ears • Alendronate (10 mg/day): 11 ears • Sodium fluoride (20 mg/day): 16 ears	6 months	After completing treatment[l]	1. MRI: Subjective signal intensity (SI) differences 2. MRI: Objective[m] signal intensity (SI) ratio of otosclerotic foci to brainstem (OFSI/BSSI)	1. MRI subjective analysis: The alendronate group showed a statistically significant decrease in signal intensity (SI)[n]. MRI objective analysis: Both treatment groups showed statistically significant decrease in SI, however the

(Continues)

TABLE 2 (Continued)

Author (year)	Study design	Number of subjects	Treatment	Duration of treatment	Last follow up	Main outcome measures	Results
							alendronate group experienced a greater decrease in SI compared to the sodium fluoride group[n].
Jan et al. (2017)[14]	Retrospective case review	7 patients (14 ears)	• 5 mg Zoledronate (parenteral) • 35 mg Risedronate (oral)[g]	• Zoledronate: single infusion • Risedronate: weekly[h]	Ranged from 61.6 to 109.1 months	1. Bone conduction pure tone threshold averages (PTA) (500, 1000, 2000, and 4000 Hz) 2. Word recognition scores (WRS)	1. BC-PTA[i] was stable in 11 ears, improved in 2 ears, and worsened in 1 ear. 2. WRS[j] was stable in 11 ears, improved in 2 ears, and worsened in 1 ear.

[a]One patient in the control group dropped out due to nausea and diarrhea.
[b]Follow-up data available for dropouts and treatment failures were included in the analyzed data.
[c]One patient in the experimental group dropped out due to nausea and diarrhea (considered treatment failure) and one patient dropped out of the study before 1 year.
[d]Pulsed doses: etidronate given daily for 1 month followed by a 2-month rest period.
[e]A total of 896 patients were treated, however only 545 patients were analyzed. Of these, only 265 presented with primary symptoms of SNHL. Other primary symptoms groups included for treatment were dizziness (426 pts), tinnitus (152 pts), and Meniere's syndrome (53 pts).
[f]Raw audiometric data was not reported. Statistical analysis of the audiometric data was not specified.
[g]Three patients preferred oral treatment and therefore received Risedronate.
[h]Duration of weekly treatment not specified.
[i]PTA significant change defined as ±10 dB.
[j]Significant change of WRS value was defined using a binomial model of variance, with significant change varying from 4% to 18% depending on the starting value.
[k]Ears that underwent prior stapedectomy were excluded from the study (10 ears).
[l]Treatment duration not specified.
[m]Objective analysis performed using the eFilm Workstation v. 3.1 software.
[n]A decrease in signal intensity demonstrates decreased activity of the otosclerotic foci.

rate of change in disease progression in the year just prior to the experiment (1-year pretreatment data) as well as the overall progression (first available data). Both the 2012 and 2017 studies used a ±10 dB as a significant change in bone conduction thresholds. Additionally, these two studies assessed statistical significance with the binomial model of variance for WRSs by Thornton and Raffin.[15] They reported the average change in bone conduction threshold 1-year after treatment was 1.0 dB which would suggest stabilization, however the average change in bone conduction threshold 1-year prior to treatment was reported as 4.3 dB, which would also fall below a significant change of 10 dB.

The other studies utilizing the same subject population were two double-blind RCTs by de Oliveira Vicente et al. in 2012[12] and 2015.[13] Unlike the Jan et al.[14] and Quesnel et al.[9] study pair, these two studies were conducted simultaneously. Only the outcome measures used to quantify disease progression differentiated the studies. There were 15 ears in the control group (group A), 11 ears in the alendronate group (group B), and 16 ears in the sodium fluoride group (group C). The treatment period was 6 months. The 2012 report compared air and bone conduction thresholds, air bone gap, speech recognition threshold, and speech discrimination between groups and within each group pre- and post-treatment.[12] There was no statistically significant difference between the pre- and post-treatment bone conduction thresholds in the treatment groups B and C. At 2000 Hz the control group had a greater mean threshold after treatment than the sodium fluoride group; however, this difference existed prior to treatment ($p = .051$). At 4000 Hz the control group had greater mean values than both treatment groups before and after treatment. There was a statistically significant decrease in bone conduction thresholds at 4000 Hz in the control group, from a mean of 50 dB to a mean of 46 dB; however, all other frequencies showed no difference post-treatment. This result suggests a slight improvement in hearing at the higher frequency in the control group with no change in the treatment groups.

Air conduction thresholds also showed no statistically significant difference between the pre- and post-treatment groups, with two exceptions; the control group did have a statistically significant decrease at 500 Hz. At this frequency, the mean pretreatment threshold was 62.33 dB which decreased to a mean of 60 dB. The sodium fluoride treatment group also saw a statistically significant improvement in air conduction thresholds after treatment at 4000 Hz. Before treatment, the mean threshold was 57.67 dB and after treatment the mean value was 54 dB.

The 2015 study by de Oliveira Vicente et al.[13] followed the same pharmacotherapy treatment as the 2012 study but used MRI image analysis to quantify disease progression. Subjective analysis of pre- and post-treatment imaging was completed by a neuroradiologist and an otolaryngologist to identify an increase, decrease, or no change in the signal intensity. The signal intensity is proportional to the activity of the otosclerosis lesion and a decrease in the signal intensity implies improvement of the disease. Objective analysis was obtained using the eFilm Workstation version 3.1 software program to calculate the signal intensity ratio between the otosclerotic foci (the region anterior to the oval window) and a normalization factor (the brainstem signal intensity). Subjective analysis showed a statistically significant decrease in signal intensity for the alendronate group compared to the control ($p = .011$) and sodium fluoride ($p = .003$) groups. The objective analysis found the placebo group was essentially unchanged with a signal intensity ratio of 0.82 and 0.79 before and after treatment respectively ($p = .401$), the alendronate group had a decrease in signal intensity ratio from 0.78 to 0.55 ($p < .001$), and the sodium fluoride group also showed a decrease in the signal intensity ratio from 0.71 to 0.60 ($p = .025$). The study included a statistical power analysis for 80%, and while there was a low power resulting from the small number of participants, the authors concluded that alendronate was superior to sodium fluoride in suppressing the activity of otosclerotic lesions. The study also concluded the software program used to objectively measure changes in osteosclerosis foci was more accurate than subjective analysis.

The longest RCT study by Kennedy et al.[10] had a treatment period of 2 years. It was a double-blind study with 12 subjects in the control group and 14 subjects in the etidronate treatment group. All the subjects had evidence of mild to moderate progressive SNHL with a greater than 10 dB loss during a 6- to 12-month period. No statistically significant difference between the control and treatment groups was found when evaluating the air conduction thresholds and average discrimination scores. The authors were unable to complete a statistical evaluation on bone conduction thresholds because only five participants from each group had sufficient bone conduction data. There were three subjects who dropped out of the study prematurely, one in the control group and two in the treatment group, all follow-up data available for these subjects were included in the analyzed data. This study concluded that etidronate may have a beneficial effect in stabilizing otosclerotic lesions.

4 | DISCUSSION

This scoping review sought to analyze the current usage of bisphosphonates in treating otospongiotic lesions and the extent of available evidence. In all the studies, it is difficult to assess the impact of bisphosphonates in treating otosclerosis.

All three randomized control trials had strong protocols; however, the main weaknesses in most of the studies included in this review, including the RCTs, is a small sample size. Because SNHL caused by otosclerosis is a rare disease, including enough subjects to reach a desired statistical power will continue to challenge future investigations. While de Oliveira Vicente's group[13] included a sample size analysis, the Kennedy et al.[10] study did not. The 2015 de Oliveira Vicente et al.[13] article found differences between the control group and experimental groups and the study suggests the changes caused by bisphosphonate therapy does exist, even with the low statistic power of the results. The small number of RCTs and the variations among the studies such as dosing, frequency, duration, and follow-up of treatment for pharmacological intervention of otosclerosis make pooling multiple study results impossible.

The 2015 de Oliveira Vicente et al.[13] study using imaging produced statistically significant differences between the treatment and control groups. However, the 2012 study[12] using audiologic data of the exact same subjects and treatment did not provide results reflecting similar findings. In fact, both RCTs using audiologic data to assess disease progression found no statistically significant difference between the treatment groups and the control groups. This raises a question of clinical significance for both bisphosphonate treatment and the utility of magnetic resonance imaging as a method to measure disease progression. The 2015 de Oliveira Vicente study shows bisphosphonate therapy does affect the structure of the otic capsule, which is measurable with MRI, however because the patients in the 2012 study did not show differences in hearing outcomes, this suggests these changes may not affect hearing to the point of being clinically significant. Otosclerosis is slowly progressive, and many patients do not notice clinical symptoms until there is increased awareness of hearing loss. The reported age of onset of otospongiotic bone formation is 15–40 years.[16] Average ages in this scoping review were approximately in the late 1940s and 1950s, with most of the studies reporting age range between 20 and 70 years. Some authors suggest a longer treatment or follow-up period is needed to capture the subtle changes in otosclerosis to collect statistically significant audiologic differences,[10] and this may be the case, but the longer 2-year Kennedy et al.[10] study was unable to find result suggesting a difference between the treatment and control groups.

There is a dearth of clinical evidence demonstrating improved hearing or halted hearing loss in human subjects, and this scoping review shows the scarcity of available research. Basic science research with animal studies,[17–19] cadaveric studies,[20] case studies,[21,22] and reports are currently the most available type of research evidence. The lack of human subject data hinders evaluation of bisphosphonate usage. Moreover, the conflicting data from higher levels of evidence such as RCTs make a definitive claim in favor of bisphosphonate use challenging.

Additionally, these studies do not demonstrate an improved outcome between usage of earlier or later generation bisphosphonates. Though Kennedy et al.[10] and de Oliveira Vicente et al.[12] had different study lengths, the number of subjects and treatment groups were similar, with usage of etidronate and alendronate respectively. While it might be anticipated that later generation would be more effective than early generation bisphosphonates, this was not observed in this review. More recent generation bisphosphonates are considered to be superior when compared with previous generation bisphosphonates[23] and have a better safety profile as the required dose is less than that of earlier generations.[24] The difference is attributed to the nitrogen-containing side chain on later generation bisphosphonates that inhibit bone resorption more readily than without this group. However, for otosclerosis, the efficacy of early compared to later generation bisphosphonates has not been assessed, nor have optimum treatment durations for bisphosphonates been studied in human subjects.

Outcome measures for bisphosphonate usage in managing otosclerosis differed between studies. This review identified hearing threshold measurements such as air conduction threshold as the most reported outcome. This scoping review included the study done by Brookler and Tanyeri,[11] which includes highly variable neurotological data and verbally reported hearing loss or improvement. Additionally, this scoping review did not exclude terms or synonyms for tinnitus, dizziness, or Meniere's disease, and these symptoms were reported in the Brookler and Tanyeri[11] article. This is attributed to otosclerosis patients experiencing neurotological symptoms as well as conductive hearing loss.[25]

Because otosclerosis typically progresses slowly, long-term clinical trials are necessary to further evaluate the usage of bisphosphonates in treating or halting otosclerosis progression. As demonstrated by the de Oliveira Vicente and colleagues in two 6-month studies published in 2012 and 2015, the earlier RCT failed to note statistically significant differences using traditional audiologic metrics; but the later study was able to demonstrate a statistically significant difference when using MRI signal intensity to quantify changes in bone activity. This suggests that a more sensitive method of measurement may allow researchers to track slight changes in otosclerosis when evaluating bisphosphonate treatment. However, the use of MRI imaging did not correlate to clinically relevant changes in hearing as was demonstrated in the 2012 publication. There has yet to be definitive and clinically significant evidence demonstrating the correlation between MRI findings and stabilization or improvement of hearing thresholds after bisphosphonate usage.. Ideally, identification of patients with first-degree relatives who have hearing loss or otosclerosis would be screened regularly for otosclerosis and given pharmacological treatment at the earliest sign of SNHL.

5 | CONCLUSION

Evaluating bisphosphonate usage in treating otosclerosis proves difficult due to the dearth and weakness of evidence. The lack of randomized controlled trials in evidence-based medicine demonstrating statistical significance complicates further analysis. Moreover, current research has yet to observe bisphosphonates as preventive therapy before symptoms arise. For patients with SNHL or those who cannot undergo stapedectomy or stapedotomy, bisphosphonate treatment may stabilize future hearing loss, but improvement is unlikely. To date, the efficacy of bisphosphonate therapy for sensorineural hearing loss caused by otosclerosis remains inconclusive.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

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