Literature Review

https://doi.org/10.1590/2317-6431-2018-2048

Audiology Communication Research
ISSN 2317-6431

Auditory alteration in osteogenesis imperfecta: systematic literature review

Alteração auditiva em osteogênese imperfeita: revisão sistemática de literatura

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ABSTRACT

Purpose: To analyze scientific publications on the hearing issue of patients with *osteogenesis imperfecta*. **Reserch strategy:** This study is a systematic literature review. The following descriptors were selected "Hearing" OR "Hearing Loss" AND "Osteogenesis Imperfecta". Two reviewers searched the Cochrane Library, Pubmed, Latin American and Caribbean Health Sciences Literature, Scopus and Embase databases. **Selection criteria:** Descriptors in Health Sciences were used and the publication period of studies was not limited. Inclusion criteria were cohort, follow-up, cross-sectional, and control studies in English language. Exclusion criteria were editorial articles, case reports, case summaries, and animal studies. Selected studies were analyzed by the STROBE Initiative and the GRADE System. **Results:** Of the 652 studies, 16 were selected. Conductive hearing loss is the most common type in the osteogenesis imperfecta (OI) population and its onset is around the second decade of life. Definition and classification for hearing loss measurement in publications with the *osteogenesis imperfecta* population present disparities among studies. **Conclusion:** This review met the objectives proposed, concluding that audiological alterations found in OI patients are of conductive, sensorineural and mixed types; conductive alterations are more common in younger patients and sensorineural alterations in older ones. The STROBE initiative partially pointed out described items and the GRADE system concluded that studies present some methodological failure.

Keywords: Hearing; Hearing loss; Ear ossicles; Osteogenesis; Osteogenesis imperfecta

RESUMO

Objetivos: Analisar as publicações científicas sobre audição em indivíduos com osteogênese imperfeita. **Estratégias de pesquisa:** Trata-se de revisão sistemática de literatura. Foram selecionados os descritores *Hearing OR Hearing Loss AND Osteogenesis Imperfecta*. Duas revisoras consultaram as bases de dados Cochrane Library, PubMed, LILACS, Scopus e Embase. **Critérios de seleção:** utilizaram-se os Descritores em Ciências da Saúde, não sendo delimitado período de publicação dos estudos. Foram critérios de inclusão estudos de coorte, seguimento, transversais, casos controle e em idioma inglês. Foram critérios de exclusão artigos editoriais, relatos/séries de casos, resumos de eventos e estudos conduzidos em animais. Os estudos selecionados foram analisados pela Iniciativa STROBE e pelo Sistema GRADE. **Resultados:** Dos 652 estudos obtidos, foram selecionados 16. A perda auditiva do tipo condutiva foi o tipo mais comum na população com osteogênese imperfeita (OI) e seu início ocorre por volta da segunda década de vida. A definição e a classificação para aferição de perda auditiva, nas publicações com a população com osteogênese imperfeita, apresentaram discordância entre os estudos. **Conclusão:** Esta revisão respondeu às perguntas a que se propôs, constatando que as alterações audiológicas encontradas em pacientes com OI são do tipo condutivo, neurossensorial e misto. Alterações condutivas são mais comuns em pacientes mais jovens e alterações neurossensoriais, em pacientes mais velhos. A Iniciativa STROBE apontou itens descritos de forma parcial e o Sistema GRADE concluiu que os estudos apresentaram alguma falha metodológica.

Palavras-chave: Audição; Perda auditiva; Ossículos da orelha; Osteogênese; Osteogênese imperfeita

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Conflict of interests: No.
Authors' contribution: ACCO data collection, tabulation, analysis and writing; ART revision and approval of the version to be published; MSM data collection, tabulation and analysis; SSC review and approval of the version to be published.
Funding: None.
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Received: July 24, 2018; **Accepted:** October 17, 2018

INTRODUCTION

Osteogenesis imperfecta (OI) is an alteration that can qualitatively or quantitatively affect the production of collagen fibers[1]. When the amount of collagen produced by the body is reduced, mild OI types are observed; when collagen quality is impaired, more serious OI types are manifested[2]. It is a disorder that causes diverse and different alterations in cells that have, in their formation, collagen fibers, resulting in tissue alterations, primarily in those rich in type I collagen[3]. Among the resulting morbidities most described in literature, bone fragility and / or deformity, imperfect dentinogenesis and hearing loss stand out[4-6].

Several studies have indicated varied prevalence of hearing loss in OI patients. In addition, there is intrafamilial variability in auditory characteristics. Pillion and Shapiro[7] found auditory alterations in 62% of patients, with predominance of sensorineural or mixed hearing loss (41%). For Swinnen et al.[8], 93.9% of evaluated patients presented hearing loss, with predominance of mixed and sensorineural loss over conductive loss. Stewart and O'Reilly[9] also found predominance of mixed hearing loss. However, neither the mutated gene, type I collagen, quantitatively or qualitatively damaged, or the mutation location in relation to the triple helix, seem to play a role in the hearing loss expression[4,10].

Over the years, several studies have been conducted on the topic of hearing in OI, but it has been found that there are no studies in literature aimed at performing a literature review on this theme. These studies are important for synthesizing knowledge about a particular subject and concentrating the available evidence, improving clinical practice. In addition, they support future research, in which gaps on the subject are still found.

AIM

The aim of this study was to analyze the results of audiological studies on *osteogenesis imperfecta* guided by the following questions: What are the audiological alterations identified in OI patients? Do these changes differ among different age groups? Do these changes differ from changes found in the general population?

Research strategy

This is a systematic literature review, whose research and analysis of articles were carried out by two researchers, who independently analyzed the results found in Cochrane Library, PubMed, LILACS, Scopus and Embase databases.

To define descriptors, the structured and trilingual vocabulary Descriptors in Health Sciences (DeCS), prepared by BIREME, for indexing scientific materials was used. Descriptors Hearing OR Hearing Loss AND Osteogenesis Imperfecta were selected.

The search for scientific materials was carried out from February to March 2017 and there was no limited period for the year of publication of studies. All titles of studies found were tabulated and those whose titles did not fit this systematic review were excluded. Subsequently, abstracts remaining in the sample were read and those that did not meet the inclusion criteria or belonged to the exclusion criteria were excluded. Finally, studies that remained in the sample were read in full, excluding those that met the exclusion criteria, or did not met the inclusion criteria. Figure 1 illustrates the exclusions.

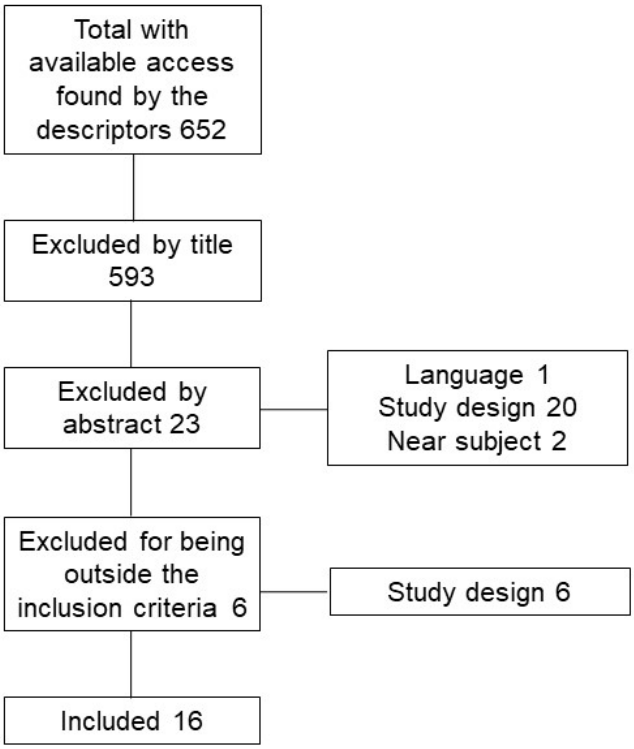

Figure 1. Article exclusions

Selection criteria

The following inclusion criteria were adopted: cohort (or cohort study), follow-up, cross-sectional and case-control studies published in English language. Exclusion criteria were editorial articles, case reports and series, researches published as case summaries and animal studies.

Data analysis

The analysis of the sixteen selected studies consisted of two phases: in the first, selected studies were read and results were tabulated; in the second, studies were analyzed according to STROBE Initiative (Strengthening the Reporting of Observational Studies in Epidemiology)[10], a methodology consisting of 22 items for the check-list of information that should be present in the article. This initiative, developed by researchers in the area of epidemiology, statistics, methodology and editors of scientific journals, aims to disseminate the principles guiding the description of studies.

The STROBE Initiative[10] provides a critical analysis of the production and dissemination of knowledge. The items

analyzed are information that should be present in the title, abstract, introduction, methodology, results and discussion of observational studies. The aim of this initiative is to contribute to the adequacy of the study report in order to provide a critical reading. The initiative is not intended to evaluate the quality of studies[10].

The analysis of the methodology of studies was performed by the GRADE system (*Grading of Recommendations, Assessment, Development and Evaluation*), developed to classify the quality of evidence and the strength of recommendations for generalization[11].

Classification using this system allows for more consistent judgments and better choices about health care, since the quality of evidence indicates the level at which it is possible to be confident that an effect estimation is correct[12]. The GRADE System considers the study design, execution, consistency of results, indirect evidence, limitations, lack of data and high probability of bias[11].

The levels of evidence are the following, according to the GRADE System[11,12]:

High (A): Consistent evidence from randomized controlled trials, with no significant limitations or exceptionally strong evidence from observational studies. It is very unlikely that further research can change confidence in the estimated effects;

Moderate (B): Evidence of randomized clinical trials with significant limitations (inconsistent results, methodological failures, inaccuracy, indirect or imprecise results), or very strong evidence from observational studies. Further studies are likely to have an impact on confidence in the effect estimate and may change this estimate;

Low (C): Evidence of at least one important outcome from observational studies, case series, or randomized clinical trials with severe failures or indirect evidence. Further studies are likely to have a significant impact on the confidence of the effect estimate and change this estimate;

Very low (C): Any effect estimate is uncertain.

RESULTS

The independent reviewers found a total of 652 articles for review, which were available at the time of selections. Articles were initially selected by title, resulting in 59 articles for subsequent abstract reading. After reading abstracts, 36 articles were left to be read in full, resulting in 16 selected articles.

In the first analysis, a table with the main information of studies was elaborated. The studies selected for this review, according to the inclusion criteria, are described in Table 1.

After reading of articles, it was possible to conclude that conductive hearing loss is the most common type of loss among OI patients, followed by an equal distribution of hearing loss of mixed type and hearing thresholds within normal pattern. In addition, 4 studies agreed that conductive hearing loss is more common in younger subjects[13,14,16,18].

Two studies also indicated that the onset of hearing loss in OI patients is around the second decade of life[15,24]. In 2 studies, it was also concluded that there is hearing loss, but there was no clear conclusion about what type of hearing loss was found[4,24]. In Tables 2 and 3, the analyses of articles are presented, according to the STROBE Initiative[10]. The analysis of studies, according to the GRADE system[11], in which all studies were given level C of evidence[4,7-9,13-24] is described.

DISCUSSION

Studies have shown that there are auditory alterations in OI patients. Conductive hearing loss is the most common loss type in the OI population and is more common in younger individuals[7,13-16,18]. Due to bone remodeling inhibition, microfractures and microlesions are likely to accumulate in temporal bones[4]. Poor ossification of the tympanic ring, ossicles, cochlea and optic capsule may also occur[13].

Mixed hearing loss type and auditory thresholds within normal pattern were present in similar percentages. Hearing loss in OI begins around the second decade of life[15,24].

The definition and classification of hearing loss type and degree, when described, vary widely among studies. It should be noted that in many of these, such criteria were not defined[4,7,9,13,15-19,24]. Thus, it is possible to conclude that there is no uniformity among forms of hearing loss evaluation in OI patients, which makes the further analyses of findings difficult.

There is no description of a specific auditory evaluation protocol to be applied to assess herring loss in OI patients in literature. Among the factors that may contribute to the diversity of protocols used are the study aims, the clinical experience of the researcher and the reality in which the study is inserted. However, the lack of a standard protocol results in very varied results, because, when classification is modified, the final result is also modified.

The onset of hearing loss in the third decade of life is in agreement with parameters for the general population[25,26]. What seems to differ in individuals with OI is that surgical intervention is necessary in many cases[16]. Case-control studies, or those comparing the hearing findings of OI patients with data from the general population are scarce[14,17,21].

Mixed type alterations were also found[8,9,21]. Commonly, hypoacusis appears as a conductive type hearing loss, between the second and fourth decade of life and, later, it evolves to mixed-type hearing loss[8]. It appears to be associated with footplate fixation due to an abnormal bone remodeling process in the temporal bone and, over time, the process progresses, also affecting the perichoclear bone and other temporal bone structures[8].

In some operated patients, fixation of the base of stapes, combined with ossicular discontinuity, was also found. According to the authors, these are the main causes of auditory alteration in OI[19]. Loss at high frequencies suggests that the cochlear basal turn is frequently involved in OI[17].

Pedersen[19] and Pedersen et al.[20] found 50% of the sample with auditory alterations. This percentage is high, since one in two patients has hearing alterations and this prevalence is much higher than for the general population. In 2012, the World Health Organization (WHO) reported that 5.3% of the world's population suffers from disabling hearing loss (above 40 dBNA for adults and 30 dBNA for children in the best ear)[27]. This result; however, may have been influenced

Table 1. Main results of selected studies

Study	Sample	Design	Definition of Hearing Loss	Main results
Bergstrom[13]	n=: 32 pediatric patients, mean age 5 years	Cross-sectional	Absent Features audiograms	CHL:14% SHL:9% MHL: 4.5%
Carruth et al.[14]	n=22 GCa n=10 GCo: n=12	Case control	Absent	In the study group, 6 people had conductive hearing loss, ranging from 20 dB to 50 dB, 1 of which was a result of otitis media.
Riedner et al.[15]	n= 70, 13 families, 5 to 48 years	Cross-sectional	Hearing loss: >25 dBHL between 250 and 8 kHz CHL: *gap* of 5 dBNA (500-4 kHz)	OI hearing loss begins in the second or third decade. In general, younger patients have CHL and the older MHL or SHL.
Shea and Postma[16]	n=43 (62 ears) age: 2 to 50 years	Follow-up	Absent	84% bilateral CHL.
Shapiro et al.[17]	n=55 OI patients, 92 family members 43 controls	Case control	NHL: drop below 15 dBHL in consecutive frequencies CHL: *GAP*≥ 15 dBHL in one or more frequencies AN: without gap presence, drop greater than 15 dBHL CHOI: SHL at high frequencies (6 and 8)	1. not only typical SHL occurs more than CHL or MHL, an atypical and characteristic SHL pattern occurs with significant frequency in OI patients and their relatives; 2. Middle ear function is also abnormal in OI, probably due to the involvement of the ligament and ossicle. The middle ear may also be abnormal in many first-degree relatives with no history of fracture; 3. These abnormalities are influenced by age.
Cox and Simmons[18]	n = 30, 5 families, ages 4 to 67 years, 57% between 4 and 20 years	Cross-sectional	Hearing loss: pure tone> 20 dBHL between 250 and 1 kHz and / or> 25 dBHL between 2 and 6 kHz	11 participants with loss, mean 26 years (9 to 67 years) Of the 11 with loss: 6 mild CHL, 2 moderate MHL and 2 mild, 1 moderate CHL at high frequencies.
Pedersen[19]	n = 201, less than 10 to more than 70 years	Cross-sectional	SHL:AC ≥15 dBHL and *gap*<15 dBHL CHL:BC >15 dBHL and *gap*≥ 15 dBHL MHL: BC≥15 dBHL and *gap*≥ 15 dBHL For frequencies from 250 to 4 kHz	NHL 50% MHL 27% CHL 12% SHL 8% Anacusia 3%
Stewart and O'Reilly[9]	n= 56, age: 10 to 60 years	Cross-sectional	SHL: VA≥ 30 dBHL on at least two frequencies between 250 and 8 kHz CHL: *gap*≥ 15 dBHL on at least two frequencies between 250 and 4 kHz MHL: BC≥ 30 dBHL and *gap*≥ 15 dBHL on at least two frequencies between 250 and 8 kHz	MHL: 16% CHL: 14% SHL: 12% NHL: 4% Results for 46 ears with tympanogram.
Pedersen et al.[20]	213 patients	Cross-sectional	Absent	50% NHL 27% MHL 12% CHL 8% SHL 3% Anacusia

Subtitle: CHL = conductive hearing loss; SHL = sensorineural hearing loss; MHL = mixed hearing loss; NHL = normal hearing thresholds; CHOI = hearing loss characteristic of OI; AC= air conduction; BC= bone conduction; dBHL= decibels Hearing Level; OI= osteogenesis imperfect; GCa = case group; Gco = control group; SD = standard deviation

Table 1. Continued...

Study	Sample	Design	Definition of Hearing Loss	Main results
Garretsen et al.[21]	142 participants with type I OI, divided into children and under 30 years of age	Case control	CHL: mean gap in 500, 1 and 2 or 4 and 8 ≥ 15 dBHL and BC <15 dBHL SHL: AC ≥ 15 dBHL, *gap* below 15 dBHL MHL: *GAP*≥15 dBHL and BC≥15 dBHL CHOI: Shapiro et al.[17]	MHL:<30 years:37% ≥30 years:68% NHL:<30 years:34% ≥ 30 years:6% SHL:<30 years:18% ≥30 years:19% CHOI:<30 years:7% ≥30 years:5% CHL:<30 years: 2% ≥ 30 years:0% Disabling:<30 years:2% ≥30 years:2%
Kuurila et al.[22]	45 children, average age: 10 years, maximum age: 16 years	Cross-sectional	NHL: AC ≤ 20 dBHL CHL: *gap*≥ 15 dBHL and BC<15 dBHL SHL: BC ≥ 15 dBHL and *gap*<15 dBHL MHL: *gap*>15 dBHL and BC ≥ 15 dBHL For mean 500-2 kHz	NHL: 93.3% The three cases of loss were 2 CHL and 1 SHL from birth, probably of etiology unrelated to OI.
Imani et al.[23]	n = 22, mean age: 9.64 years	Cohort	Not described. Presents altered audiometry results	Incidence of loss: 77.3% Losses were of conductive component that was solved and 5 children with permanent loss, 3 SHL and 2 CHL.
Paterson et al.[24]	n: 1.394 0 to 70 years	Cross-sectional	Absent	The onset of loss between the second and fourth decade of life was more common. At age 50, approximately 50% had loss. In the next 20 years, there was little increase. Hearing loss was significantly lower in type IV OI than in type I OI.
Pillion and Shapiro[7]	n=41 Groups: >20 years (n=21) <20 years (n=20) Mean age: 26.54 (2 to 68 years)	Cross-sectional	SHL: AC>20 dBNA 250 to 8 kHz and *gap*<10 dBNA from 250 to 4 kHz CHOI: *gap*<10 dBNA from 250 to 4 kHz e high threshold from 6 to 8 kHz CHL: AC>20 dBNA and *gap*>10 dBNA from 250 to 4 kHz MHL: AC>20 dBNA and BC>15 dBNA with *gap*>10 dBNA from 250 to 4 kHz	loss of 62% ears; prevalence> 20 years: 88%; <: 38% SHL or MHL: 41% CHL: 21% In children (mean age 9.87 SD: 4.33) CHL is predominant and in adults (mean age: 44.05 SD: 12.44) MHL is predominant.
Swinnen et al.[4]	n = 184, mean age: 30.5 (3 to 89 years).	Cohort	NHL: AC<15 dBNA in 500, 1 and 2 CHL: BC<15 dBNA and *gap*≥15 dBNA on average of 500, 1 and 2 SHL: AC≥15 dBNA and *gap*<15 dBNA on average of 500, 1 and 2 or AC>30 dBNA on average of 4, 6 and 8 MHL: BC≥15 dBNA and *gap*≥15 dBNA on average of 500, 1 and 2	Loss in 52.7% 44% bilateral 8.7% unilateral
Swinnen et al.[8]	n=56	Cross-sectional	NHL: AC<15 dBNA CHL: BC<15 dBNA and *gap*>15 dBNA MHL: BC>15 dBNA and *gap*>15 dBNA SHL: AC>15 dBNA and *gap*<15 dBNA Deafness: AC>20 dBNA	39% NHL 21% MHL 11% SHL 4% SHL high frequency 3% CHL

Subtitle: CHL = conductive hearing loss; SHL = sensorineural hearing loss; MHL = mixed hearing loss; NHL = normal hearing thresholds; CHOI = hearing loss characteristic of OI; AC= air conduction; BC= bone conduction; dBHL= decibels Hearing Level; OI= osteogenesis imperfect; GCa = case group; Gco = control group; SD = standard deviation

Table 2. Analysis of the distribution of articles that described the methods in whole or in part according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE Initiative)

Variables	Total n(%)	Partial n(%)
Study design	6 (37.5)	10 (62.5)
Context	6 (37.5)	10 (62.5)
Participants	5 (31.25)	11 (68.75)
Variables	4 (25)	12 (75)
Source of data/Measurement	8 (50)	8 (50)
Bias	4 (25)	12 (75)
Study size	5 (31.25)	11 (68.75)
Quantitative variables	4 (25)	12 (75)
Statistical methods	2 (12.5)	14 (87.5)

Table 3. Analysis of the distribution of articles that described discussion items in whole or in part in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE Initiative)

Variables	Total n(%)	Partial n(%)
Limitations	3 (18.75)	13 (81.25)
Interpretation	4 (25)	12 (75)
Generalization	1 (6.25)	15 (93.75)

by the sample characteristics and by the collection protocol (definition of hearing loss adopted) and data analysis adopted.

Regarding the pathogenesis of auditory alterations, the main causes of conductive alterations described were limitations of the mobility of middle ear structures[15,28-30]. For sensorineural changes, the involvement is not yet fully understood[7,19,31]. However, changes in optic capsule structures, which interfere with cochlear function, have been reported[4,7,8,17,32-35].

Analysis by the STROBE Initiative[10] has shown that, in general, the description of methods was performed in a partial way. The majority of studies have incompletely described their design. It is worth mentioning that describing the design is essential for understanding the work and for other researchers to replicate the study. Classifying the design, although it may be a difficult task, is advisable[36].

The "study size" item of the STROBE Initiative refers to criteria and data for determining sample size. None of the studies presented the sample calculation description. This stage is fundamental so that inferences for the rest of the OI population are made. Evaluating a random sample of the population is often difficult, but in this way, the study generalizability is increased[36].

In addition, other aspects such as inclusion and exclusion criteria and sampling type were not fully described in some studies[4,7,14,15,17,21,22,24], but fully described in others[8,9,13,16,18,23]. This information is important for the complete understanding of studies and their reproducibility.

Statistical methods and procedures for obtaining variables were also partially described in some studies[7,9,15,24]. However, they were completely described in other studies[4,8,17,21]. Specifically when it comes to audiology, the forms of measurement should be described, so that a critical analysis of findings can be performed and, mainly, studies can be reproduced and compared. The evaluation of previous studies on OI is difficult due to the variable definitions of hearing loss[22].

According to the analysis of studies by the GRADE System, it was concluded that studies had level C of evidence, since all presented some methodological failure. Some did not describe the hearing loss definition[13-15,20,23,24] and none described the possibility of generalization, as was verified by the sample calculation[4,7-9,13-24].

CONCLUSIONS

This literature review met the objectives proposed, finding that:

- Audiological alterations found in OI patients were conductive, sensorineural and mixed;
- Alterations differed among age groups, with conductive alterations being more common in younger patients and sensorineural alterations in older patients;
- Audiological alterations in OI patients differed from the general population, since they are more prevalent and their course often culminates in surgical treatment.

Studies on hearing loss in the OI population; however, are not exhausted. There are still doubts about the development and evolution of hearing loss in this population. The elaboration of a protocol for evaluation and diagnosis of hearing disorders in OI patients and new studies on the subject are suggested.

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