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*Official Journal of the Italian Society
of Otorhinolaryngology Head
and Neck Surgery*

Organo Ufficiale della Società Italiana
di Otorinolaringoiatria
e Chirurgia Cervico-Facciale

Advances in otosclerosis

Edited by Stefano Berrettini



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Advances in otosclerosis

Introduction

This monograph focuses on the significant advances in the diagnosis and treatment of otosclerosis, a disease that has long been at the centre of otologic research and clinical practice. The papers presented in this Supplement reflect the efforts of the Otolaryngology Unit at the University of Pisa, which has placed stapes surgery at the core of its activities for over five decades.

The collection of articles underscores the multidisciplinary approach necessary to tackle the complexities of otosclerosis, spanning from genetic research and audiological diagnosis to imaging techniques and surgical interventions, including cochlear implantation and implantable hearing aids. From this viewpoint, the most current and debated topics regarding this pathology are also addressed: pathogenesis and histopathology, surgical indications, the role of radiology and innovative imaging techniques, differential diagnosis, traditional and laser surgical techniques, complications, and revision surgery.

By bringing together insights from genetics, audiology, imaging, and surgery, we aim to offer a comprehensive overview of both the challenges and opportunities in managing this complex condition.

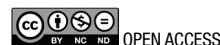


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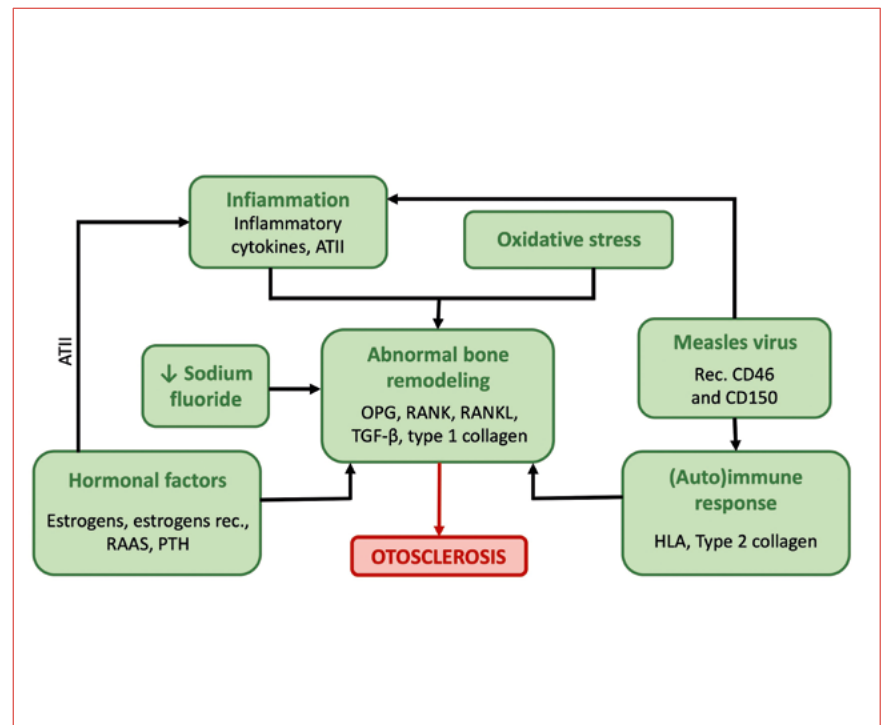


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Exploring the genetic landscape of otosclerosis: current understanding and future perspectives

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Cover figure. Model for the pathophysiology of otosclerosis. ATII: angiotensin II; OPG: osteoprotegerin; RANK: receptor activator of nuclear factor-kappa B; RANKL: ligand of RANK; RAAS: renin-angiotensin-aldosterone system; PTH: parathyroid hormone; HLA: human leukocyte antigen; TGF: tumour growth factor; CD: cluster of differentiation.

Summary

Otosclerosis is characterised by abnormal bone remodelling in the otic capsule, leading to progressive hearing loss. Unlike many genetic disorders, the causative genes for otosclerosis remain largely unidentified despite extensive research using linkage analysis and genome-wide association studies (GWAS). Inheritance patterns in otosclerosis suggest a multifactorial model involving genetic predisposition and environmental triggers, a model applied to other common diseases, such as age-related hearing loss, coronary artery disease, and Alzheimer's disease. Linkage analysis has identified nine loci associated with monogenic forms of otosclerosis, yet the specific causative genes and variants remain elusive. Promising insights have emerged from GWAS, with strong associations identified for novel candidate regions, including the *RELN* gene. Recent studies using next generation sequencing have identified several candidate genes such as *SERPINF1*, *ACAN*, and *MEPE*. *SERPINF1*, encoding pigment epithelium-derived growth factor, is linked to regulation of angiogenesis in bone remodelling. *ACAN*, associated with the *OTSC1* locus, encodes aggrecan a crucial component of the extracellular matrix in cartilage, showing a range of variants with varied

effect sizes and frequencies. MEPE, involved in bone homeostasis, has been significantly associated with otosclerosis in large family-based and case-control cohorts. While considerable progress has been made in identifying potential genetic contributors, the precise genetic architecture of otosclerosis remains to be fully elucidated. An integrated approach combining genetic data and clinical information, such as audiometric testing and temporal bone imaging, is essential for a comprehensive understanding of otosclerosis.

Key words: genetics, otosclerosis, genome-wide association studies, susceptibility, next generation sequencing

Introduction

Otosclerosis is a disease of bone remodelling that results in localised bone dysplasia within the otic capsule, causing progressive conductive hearing loss in 90% of affected patients, with a sensorineural or mixed component in the remaining 10%¹. Reports of hereditary conductive hearing loss, consistent with clinical otosclerosis, date back to the late 19th century². Subsequent studies have identified patterns of inheritance, including autosomal dominant with incomplete penetrance (about 25-40%)³ and a digenic pattern⁴. Nevertheless, families exhibiting a clear Mendelian-like autosomal dominant inheritance of otosclerosis are uncommon, as the majority of cases of otosclerosis with a positive family history (50-60%) do not adhere to clear Mendelian patterns, while the remainder (40-50%) are sporadic with no family history of the disease⁵.

Among the numerous models to explain the inheritance patterns of otosclerosis, the most likely explanation lies in complex (multifactorial) inheritance, entailing a combination of genetic susceptibility genes and environmental factors, and their interactions, a model proposed for many other diseases, such as age-related hearing loss, Alzheimer's, and coronary artery disease¹. However, monogenic and complex inheritance models should not be considered as separate entities, but as part of a continuum spectrum where the different genetic variants can be ordered, ranging from very rare ones with a large size effect and an almost perfect Mendelian segregation, to common variants with low effect sizes that act as susceptibility factors in a more complex and multifactorial aetiological pattern. In this model, genetic susceptibility factors interact with environmental triggers to generate the pathological phenotype. Among the possible environmental risk factors for the development of otosclerosis, infection with measles virus, low sodium fluoride in drinking water, and endocrine factors are under investigation (Cover figure).

Epidemiologically, the incidence of otosclerosis is higher in Caucasian patients of European descent, showing a prevalence of 0.2-1% in the general population⁵, whereas it is rare among Africans, Asians, and American Indians⁶. This disparity may reflect differences in genetic contributions and environmental risk exposures. Additionally, otosclero-

sis is more prevalent in females than males, at a ratio of about 2:1. This observation suggests a potential role for sex hormones in the development of pathologic otic capsule dysplasia.

Bone remodelling is a fundamental biological process that is essential for repairing bone damage, preventing the accumulation of aged bone – which may lose its flexibility and become brittle – and creating a reservoir for calcium and phosphorus. The efficacy of bone remodelling lies in the dynamic equilibrium between bone resorption and deposition. This balance is achieved through the spatially coordinated, integrated, and sequential actions of osteoclasts and osteoblasts, which collectively form a basic multicellular unit. This process is tightly regulated by various factors, including osteoprotegerin (OPG), receptor activator of nuclear factor-kappa B (RANK), and its ligand (RANKL)⁷. Mesenchymal-derived bone-forming osteoblasts express and secrete RANKL in response to a variety of hormones, cytokines, and mechanical stimuli. Upon secretion, RANKL binds to its receptor RANK on monocyte progenitor stem cells (MPC), initiating their differentiation into mature, active osteoclasts. These osteoclasts, which fuse into multi-nucleated cells, are responsible for bone resorption by secreting lysosomal enzymes, such as collagenases, and hydrochloric acid, capable of dissolving hydroxyapatite, one of the main acellular components of bone tissue. The activation and differentiation of osteoclasts through RANKL are neutralised by the decoy receptor OPG, also secreted by osteoblasts⁸. Conversely, bone repair is initiated by osteoblasts that secrete the osteoid seam in the lacunae created by osteoclasts. Calcium and phosphate ions then deposit in the form of hydroxyapatite, effectively trapping the secreting osteoclasts, which differentiate into osteocytes. An imbalance of the OPG/RANKL ratio has been implicated in various bone disorders, such as osteoporosis, rheumatoid arthritis, and bone metastases⁹, while inactivating mutations in the OPG gene have been demonstrated to cause juvenile Paget's disease of bone¹⁰.

The unique biology of otic capsule

The dense tissue of the petrous temporal bone that surrounds the membranous labyrinth of the inner ear is known

as the osseous labyrinth or otic capsule. It has long been recognised as a histologically unique bone, characterised by the highest bony density in the body ¹¹, and a rate of growth, modelling, and remodelling that is minimal compared to other bones, and virtually absent close to inner ear spaces ¹²⁻¹⁴. The primary foetal bone in the otic capsule is compact, highly mineralised ¹⁵, and formed by endochondral ossification, a process that involves a cartilaginous precursor which is resorbed and replaced by dense lamellar bone. Bone turnover rates in the adult temporal bone increase centrifugally from 0.1%/year in the innermost perilabyrinthine zone – where epifluorescence demonstrated a persistence of early foetal bone around the inner ear spaces in a rabbit animal model ¹⁶ – to about 10%/year at the capsule periphery, a rate comparable to other bones in the body ^{13,16,17}. These observations suggest the existence of a local inner ear mechanism that inhibits perilabyrinthine bone resorption and remodelling.

In 2010, Stankovic and colleagues ¹⁸ used real-time quantitative polymerase chain reaction (RT-PCR) and in-situ hybridisation to compare gene expression between the healthy adult murine otic capsule and other bones in the body, particularly the tibia (formed by endochondral ossification like the otic capsule) and the parietal bones (formed directly by intramembranous ossification without an intermediate tissue). They found that the molecular profile in the otic capsule significantly differs from the other bones, involving a reduction of pro-inflammatory cytokines, an increased expression of anti-inflammatory cytokines, and a distinct pattern of expression of bone morphogenic proteins (BMP). The key predictors of otic capsule bone were OPG, bone morphogenic protein receptor 1B (BMPRI1B), and bone morphogenic protein 3 (BMP3).

The increased expression of OPG is the most characteristic marker of the otic capsule, as established in numerous studies ¹⁹⁻²³, and is expressed 1600 times more in the spiral ligament and 800 times more in the fluid-filled inner ear space than in other bones in the body ¹⁹ and associated with a marked inhibition of bone remodelling within the otic capsule. OPG is expressed at high levels by cochlear neurons of the inner ear and then diffuses into the surrounding otic capsule, being a central regulator not only of bone resorption inhibition but also of neurite growth stimulation. A possible explanation for the central role of the OPG-RANK-RANKL pathway in the dynamic interaction between the skeletal and nervous systems is provided by the hypothesis that RANKL may activate the expression of neurite growth inhibitor A (Nogo-A), which, when expressed, has been associated with a dramatic shortening of spiral ganglion

nuclei neurites ^{23,24}. Therefore, the competitive inhibition of RANKL by OPG has the potential to inhibit bone remodelling and favour nerve growth, aiming to prevent nerve compression by bone growth in the otic capsule. Conversely, during the early postnatal development of the inner ear, bone remodelling is active in otic capsule development and nerve growth is inhibited ²³. OPG knockout mice (OPG^{-/-}) demonstrated a degeneration of the cochlear nerve with progressive sensorineural hearing loss (SNHL) that was superimposed on a form of earlier conductive hearing loss due to resorption of ossicles in the middle ear ^{19,21,25}. The mechanism of apoptosis caused by the loss of OPG in spiral ganglion neurons likely involves the ERK signalling pathway, an important regulator of myelination that makes neuron cells more sensitive to oxidative stress ²⁵. In OPG^{-/-}, this process can be rescued with medical therapies involving the administration of exogenous OPG, ERK inhibitors, or bisphosphonates ²⁵. Alterations in the expression of OPG have been associated with diseases such as osteopetrosis ²⁶, osteoporosis ²⁷, otosclerosis ^{19,28}, juvenile and adult Paget's disease of bone ²⁹, and celiac disease characterised by high-turnover osteoporosis ³⁰.

BMPs play an essential role in skeleton development and repair, and have been reported to be important for otic capsule formation and maintenance of the membranous labyrinth ^{31,32}. Conversely, inhibition of BMP by noggin has been associated with a loss of the otic capsule and membranous epithelium in an avian model ³². BMPRI1B is histologically unique to the otic bone, characterised by endochondral formation, while it is absent in parietal bones, intramembranous bones whose development does not involve a cartilage intermediate ¹⁸. A lower expression of BMP3 is characteristic of the otic capsule compared to other bones ¹⁸. It is the most abundant BMP in adult trabecular bone, being a negative regulator of bone density ³³; considering that the otic capsule is the densest bone in the body, the down-regulation of BMP3 is coupled with the reported increase in bone density. However, when comparing BMP3 knockout mice ³³ with BMP3 over-expressor mice ³⁴, no gross abnormalities within the otic capsule or the cochlear membranous labyrinth were reported, concluding that BMP3 has a minimal role in controlling bone remodelling in the otic capsule ¹⁸. The downregulation of inflammation is a key molecular feature of the otic capsule, and is possibly important in the maintenance of normal hearing. Proinflammatory cytokines in the cochlea are generally considered markers of disease and have been associated with hearing loss, with anatomical communication between the otic capsule and the cochlea perilymph ¹⁹, and with pathological new bone for-

mation within the membranous labyrinth (labyrinthitis ossificans)³⁵. Consistently, when comparing the healthy adult murine otic capsule and other bones in the body, Stankovic and colleagues³⁶ reported a lower expression of pro-inflammatory cytokines (TNF α , IL1 α , IL1 β , IL6, NFK β 1) and an increased expression of anti-inflammatory cytokines (particularly IL11) in the otic capsule.

Monogenic and familial forms of otosclerosis

Gene identification in otosclerosis depends on the mode of inheritance, distinguishing between confirmed familial (possibly monogenic) cases and those with a complex (likely multifactorial) inheritance pattern. For large families with numerous members affected, gene identification relies on linkage analysis to pinpoint the disease-causing variant by highlighting the chromosomal region shared by all affected individuals within a family. The effectiveness of this method hinges on the size and structure of the family selected for study. Typically, hundreds to thousands of genetic markers, which segregate in a Mendelian fashion, are analysed in a chromosomal region common to all affected family members, effectively acting as a monogene. Once the region of interest is identified, it is possible to refine the candidate loci using additional markers or genetic databases, and suspected genes can be examined through mutation analysis. Although this approach has identified nine different loci (Tab. I), pinpointing causative genes has been challenging, with only two candidate genes: T-cell receptor beta (TRB locus) identified in the OTSC 2 region on chromosome 7³⁶ and FOXL1 recently identified on chromosome 16 in OTSC 11 locus³⁷. However, even in this instance, the variants responsible for the disease remain unidentified.

OTSC 1

The first locus associated with familial otosclerosis was reported by Tomek and colleagues in 1998³⁸. In their analysis, they explored the impact of age on disease progression, noting that the sensorineural component of HL worsened in older subjects, whereas conductive HL did not significantly differ between younger and older subjects. Further genetic linkage analysis using short tandem repeat polymorphisms (STRPs) yielded a maximum multipoint logarithm of odds (Lod) score of 3.4³⁸. The Lod score, a statistical method used to assess linkage, evaluates the likelihood of a given sequence of genetic events occurring if the loci are linked as compared to its occurring if the loci are not linked. Link-

age is considered to be established if the Lod score exceeds 3. Subsequent genetic analyses restricted the linked region to a 14.5 centimorgan (cM) segment between the far and near centriole segments of the long arm of chromosome 15 (D15S657). This region contains the gene for aggrecan (ACAN), the primary non-collagenous component of the cartilaginous extracellular matrix^{39,40}.

OTSC 2

The OTSC 2 region on chromosome 7 harbours some known genes, such as TIF1a (transcription intermediary factor 1-alpha), and PLOD3 (procollagen-lysine, 2-oxyglutarate, 5-dioxygenase 3)⁴¹. TIF1 is a growth suppressor required for the activity of retinoic acid, which has been shown to disrupt the development of the otic capsule⁴². PLOD3 takes part in the biosynthesis of collagen, and in vitro expression studies have shown that PLOD3 hydroxylates lysyl residues in collagen sequences in non-triple-helical conformation. Moreover, PLOD3 activity is enhanced by tumour necrosis factor-alpha (TNF α), which is a key mediator in the pathogenesis of arthritis, causing cartilage degradation and joint destruction⁴³. Moreover, the region harbours T-cell receptor beta (TRB locus), which is one of the candidate genes for which evidence of association with otosclerosis was provided by Schrauwen and colleagues^{1,36}, describing a lower mRNA expression of TCR-beta and a decreased percentage of circulating TCR-alpha/beta-positive T cells in patients with otosclerosis linked to OTSC2 compared to controls and patients with a complex form of the disease. Further analysis showed significant disturbances in specific T-cell subsets, including an increased population of CD28null T cells in OTSC2 patients, which are considered senescent cells and whose higher proportion may indicate an altered T cell development or aging in OTSC2 patients. Overall, these findings may contribute to elucidate a possible immunological contribution to the development of otosclerosis. However, the pathological TCR-beta variant responsible for this phenotype could not be identified.

OTSC 3

The region 6p21.3-22.3 on chromosome 6 (identified as OTSC 3) includes candidate genes such as RING1 and COL11A2⁴⁴. Overall, these genes may provide insights into the association of otosclerosis with collagen abnormalities. RING 1 together with Yin Yang 1 binding protein (RYBP) interacts with Yin Yang 1 (YY1)⁴⁵, a transcription factor activator of the COL1A1 (collagen type 1) promoter in fibroblasts⁴⁶. An abnormal COL1A1 transcription may impact the normal stoichiometry of COL1A1 and COL1A2 in the

Table I. Loci associated with monogenic and familial forms of otosclerosis.

Locus	Position	Study	Investigated candidate genes	Family countries of origin
OTSC 1	15q25-26 (14.5 Mb)	Tomek et al., 1998	/	Southern India, Tunisia
OTSC 2	7q34-36 (16 Mb)	Schrauwen et al., 2010; Van Den Bogaert et al., 2001	TRB locus, ATP6V0A4, CLEC5A, EPHA1, EPHB6, HIPK2, KLRG2, LUC7L2, MKRN1, PIP, PRSS2, SSBP1, TRIM24, TRPV5, TRPV6	Belgium, England
OTSC 3	6p21.3-22.3 (17.4 Mb)	Ali et al., 2007; Chen et al., 2002	/	Cyprus, Tunisia
OTSC 4	16q21-23.2 (10 Mb)	Brownstein et al., 2006	/	Israel
OTSC 5	3q22-24 (15.5 Mb)	Van Den Bogaert et al., 2004	PCOLCE2, CHST2	The Netherlands
OTSC 7	6q22.3-6q23.3 (16.5 Mb)	Thys et al., 2007	COL12A1, COL9A1	Greece, The Netherlands
OTSC 8	9p13.1-q21.11 (34.16 Mb)	Bel Hadj Ali et al., 2008	TJP2, TRPM3, KLF9	Tunisia
OTSC 10	1q41-44 (26.1 Mb)	Schrauwen et al., 2011	TGFB2, AGT	The Netherlands
OTSC 11	16q24.1 (9.96 Mb)	Abdelfatah et al., 2022	FOXL1	Canada

production of collagen trimers, as exemplified by osteogenesis imperfecta, a disease also characterised by fixation of the stapes footplate.

COL11A2 is a putative collagen-modulating element gene expressed in the otic capsule that causes autosomal dominant non-syndromic HL at the DFNA13 locus ⁴⁷. Moreover, the region contains human leukocyte antigens (HLA) genes, consistent with the reports of a significant association of certain HLA-A and HLA-B antigens with otosclerosis ⁴⁸.

OTSC 4

The OTSC 4 region on chromosome 1649 involves several genes related to bone homeostasis or immune development, including members of the cadherin superfamily (transmembrane proteins that mediate cell recognition and cell-cell adhesion), of the conserved oligomeric Golgi (COG) multiprotein complexes, involved in intracellular membrane trafficking and expressed in the immune system, and of members of the DEAD (Asp-Glu-Ala-Asp) box proteins, involved in RNA transcription, translation, export and turnover, and ribosome and spliceosome assembly ⁴⁹.

OTSC 5

The OTSC 5 region on chromosome 3 involves two candidate genes: procollagen COOH-terminal proteinase enhancer protein 2 (PCOLCE2) and carbohydrate sulfotransferase 2 (CHST2). The *PCOLCE2* gene product is a glycoprotein that binds the COOH-terminal propeptide of type I procollagen and is highly expressed in non-ossified cartilage in developing tissues. The *CHST2* gene product is a Golgi-associated sulphotransferase, with a possible role in intercellular communication. However, mutation analysis of the coding region and the intron-exon boundaries of both genes did not reveal any disease-causing mutation ⁵⁰.

OTSC 7

The candidate gene in the OTSC 7 region in chromosome 6 is represented by COL12A1 (collagen type II alpha 1) which belongs to the fibril-associated collagens with discontinuous triple helices, and is expressed in the cochlea, while further mutation analyses failed to reveal any disease-causing mutation ⁵¹.

OTSC 8

Among the genes in the OTSC 8 region on chromosome 9,

Bel Hadj Ali and colleagues⁵² described three possible candidates: tight junction protein 2 (TJP2), transient receptor potential cation channel, subfamily M, member 3 (TRPM3), and kruppel like factor 9 (KLF9). TJP2 belongs to the family of membrane-associated guanylate kinase (MAGUK) homologues, which take part in epithelial and endothelial intracellular junctions. TRPM3 is a cation-selective channel important for cellular calcium signalling and homeostasis and for osteoclast activity. KLF9 is a strong activator of activating enhancer binding protein 2 alpha (AP-2), which is a fundamental regulator of the mammalian craniofacial development.

OTSC 10

The region on chromosome 1 identified by Schrauwen and colleagues⁵³ and named OTSC10 contains 306 gene predictions, including two candidate genes: transforming growth factor beta 2 (TGFB2) and angiotensinogen (AGT), selected due to their known role in bone remodelling and on the basis of previously found associations with otosclerosis^{51,55}.

OTSC 11

In a recent study, Abdelfatah and colleagues³⁷ identified on chromosome 16 a novel OTSC locus (OTSC 11) in a Caucasian family of English extraction with a form of autosomal dominant otosclerosis who had previously tested negative for shared OTSC loci haplotypes and susceptibility genes (*COL1A1*, *COL1A2*, *NOG*), and for rare variants associated to the *SERPINF1* gene. Sanger sequencing for 12 positional candidate genes identified an in-frame deletion in *FOXL1* (NM_005250.3: c.976_990del) associated with the phenotype in the affected family, resulting in a significant loss of the protein's helical structure. FOX proteins are a superfamily of transcription factors with a wide range of functions at the junction of multiple signalling pathways, with crucial roles in regulating gene expression in cell metabolism, proliferation, differentiation, and apoptosis⁵⁶.

Unsuccessful sequencing of functional candidate genes

To identify candidate genes of monogenic forms of otosclerosis, direct sequencing of positional candidate genes has been applied. The selected genes were prioritised based on phenotypic similarities between otosclerosis and related diseases. For example, *NOG* mutations cause several syndromes which share the presence of stapes ankylosis⁵⁷, while *COL1A1* and *COL1A2* encode alpha chains of collagen type 1, and when mutated cause osteogenesis imper-

fecta⁵⁸, which is characterised by a form of HL resembling otosclerosis (progressive, developing from the second-third decade of life, often both conductive and sensorineural). However, despite the resemblance with otosclerosis, this approach did not identify any disease-causing mutation⁵⁸. Despite the 20-year lapse since the mapping of *OTSC1*, the *OTSC* genes remain refractory to discovery due to the rarity of monogenic families, diagnostic challenges, and reduced penetrance. However, the application of new approaches (such as positional cloning and next generation sequencing, NGS) as applied in the recent work by Abdelfatah et al.³⁷ on OTSC 11, may produce successful results in identifying all *OTSC* genes, which remains a fundamental step in clarifying the genetic landscape of otosclerosis.

Complex forms of otosclerosis

Although otosclerosis appears to follow a Mendelian-like autosomal dominant pattern in some isolated families, most hereditary forms of the disease result from a complex transmission. In these cases, no single genetic susceptibility factor is either necessary or sufficient to develop the phenotype; rather, it is the combination of all factors that is crucial. The typical research method to identify genetic variants of complex diseases involves candidate gene-based association studies using a case-control design. This approach, which identifies variants of selected genes that are significantly more frequent in patients than in matched controls, has been performed in numerous studies. Some genes have been found to be significantly associated with otosclerosis in more than one study, while associations with other candidate genes have not been replicated. However, lack of replicability does not necessarily rule out an association, as the sample size might have been inadequate, or different disease-causing variants may be present in different populations. The most recent alternatives to candidate gene-based association studies are genome wide association studies (GWAS) and microarray gene expression studies, which compare gene expression in diseased tissues to that in controls. With the latter method it was possible to identify different pathways to which otosclerosis susceptibility factors seem to belong, including bone remodelling and immunological, inflammatory, and endocrine pathways.

Altered bone metabolism

Collagens

The first study to hypothesise a common genetic basis between otosclerosis and osteogenesis imperfecta type 1

(caused by mutations in type 1 collagen) was published in 1998 by McKenna and colleagues⁵⁹. They provided a rationale for this association based on the similarities in histopathology and HL features between the two diseases. This initial case-control genetic association study demonstrated a significant association of clinical otosclerosis with mutations of COL1A1 in a small population of European descendants in Massachusetts. These findings were later confirmed by the same group⁶⁰, which further identified an association with otosclerosis for polymorphisms in the first intron of the Sp1 binding site of COL1A1, a finding also recently reported by Zhang and colleagues⁶¹. In 2007, Chen et al.⁶² confirmed these results and reported an association with polymorphisms that alter the binding of transcription factors regulating COL1A2, leading to an increase in COL1A1 homotrimers and a subsequent abnormal bone deposition in the otic capsule. Normally, collagen type 1 triple helices are composed of COL1A1 and COL1A2 in a 2:1 ratio, whereas COL1A1 homotrimers are rare. Associations of otosclerosis with COL1A1 have been reported in numerous studies^{63,64}, but not in others^{65,66}, and, more relevantly, were not reported in a meta-analysis of GWAS studies of otosclerosis in three population-based biobanks comprising 3,504 cases and 861,198 controls⁶⁷. Instead, this meta-analysis reported a significant association with a subunit of collagen type 4 (COL4A2), a collagen form located in the basement membrane and highly conserved across species. Mutations in other subunits of collagen type 4 have been linked to Alport syndrome, which is characterised by progressive SNHL, nephritis, and histologically by an abnormal basement membrane and dysmorphogenesis of the organ of Corti. Future studies will need to determine the role of COL4A2 as a structural or signalling element in the context of otosclerosis.

Transforming growth factor-beta (TGF- β) superfamily

The TGF- β superfamily is composed by cytokines playing a crucial role in embryonic development and maintenance of the otic capsule⁶⁸, as demonstrated by its influence on the expression of glycosaminoglycans, fibronectin, and collagen in the extracellular matrix⁶⁹. The most relevant member of the TGF- β superfamily in the context of otosclerosis is TGF β 1, a major osteogenic cytokine involved in regulating bone mass and bone matrix. TGF β 1 is expressed in the otosclerotic foci and the hyalinised spiral ligament⁷⁰. It induces several processes in connective tissues, including the promotion of collagen type 1 and fibronectin formation⁷¹, interference with potassium circulation by affecting fibrocytes in the spiral ligament⁷², induction of chondrogenesis

in the otic capsule mesenchyme, and the promotion of otic capsule growth during early stages of inner ear development⁷³. A large association study⁵⁴ reported the Thr263Ile substitution to be significantly more expressed among otosclerosis patients than controls both in a Belgian-Dutch and in an independent French sample, and these results were replicated also in Tunisian⁷⁴, Hungarian⁶⁶ and British studies⁶⁷, but not in a black South African population⁷⁵. Additionally, sequencing the exons and intron-exon boundaries of TGF β 1 in 755 patients with otosclerosis and 877 controls revealed three rare nonsynonymous variants in four patients⁷⁶, which were not present in the controls (c.G86A, p.Gly29Glu; c.G86C, p.Gly29Ala; c.C722T, p.Thr241Ile). An analysis in an Indian sample linked the c.-509C > T single nucleotide polymorphisms (SNP) with otosclerosis, as well as a specific G-T-T-G haplotype constructed from four SNPs⁷⁷. A de novo mutation in the promoter region was also discovered in one patient, leading to decreased expression of TGF β 1⁷⁷. A study on proteomic analysis and immunostaining of temporal bones, conducted by Richard and colleagues⁷⁸, identified TGF β 1 as being expressed in patients affected by cochlear otosclerosis and hyalinisation of the spiral ligament.

The mechanism by which TGF β 1 contributes to the pathogenesis of otosclerosis remains unclear. However, one theory suggests that TGF β 1 may influence the globuli interossei within the otic capsule (residual cartilage rests within the dense bone of the otic capsule, a unique feature of the inner ear), potentially targeting these structures for an immune reaction that results in otosclerosis⁷⁸.

A meta-analysis of GWAS studies involving 3,504 cases and 861,198 controls⁶⁷ confirmed the association between TGF β 1 and otosclerosis, identifying the intronic variant rs8105161 as the strongest. Additionally, the analysis highlighted the potential roles of other genes in the TGF β 1 signalling pathway. These include RUNX2, a transcription factor essential for osteoblast and chondrocyte differentiation, regulated by TGF β 1⁷⁹. RUNX2 was found to be expressed only during the development of the otic capsule and not in its mature state. This is a critical finding, as otosclerosis may be triggered by globuli interossei, embryonic remnants within the otic capsule. Other significant genes are SMAD3 (a downstream transcription factor), CD109 (a TGF β 1 co-receptor acting as a negative regulator of the TGF β 1 pathway), LTBP3, which regulates the latency and activation of TGF β 1 through direct extracellular binding, and AHSN, which antagonises TGF β 1 signalling and directly affects the mineralisation process by inhibiting calcium phosphate precipitation. Mutations in AHSN can cause multiple-syn-

ostosis syndrome, which is characterised by stapes fixation, an otologic presentation that mimics otosclerosis⁵⁷. In a microarray analysis of otosclerotic stapedial footplates and controls, Ealy and colleagues⁸⁰ identified two other genes within the TGF β 1 pathway that are significantly expressed in both groups: PF4, which selectively prevents TGF β 1 from binding to its type I receptor and may inhibit bone resorption if overexpressed by downregulating TGF β 1 signalling, and IBSP, which is influenced by TGF β 1 signalling in rats and has been found to be downregulated in otosclerosis, along with TGF β 1.

Bone morphogenic proteins

BMP2 and BMP4 also belong to the TGF β 1 signalling network and are crucial in various molecular processes, including bone homeostasis⁸¹. A study by Schrauwen⁸² identified a correlation between otosclerosis and specific SNPs: rs3178250T > C in the 3' UTR of BMP2 and rs17563, p.(Val152Ala) in BMP4. These SNPs were analysed in an Indian population, with only the BMP4 SNP showing a significant association⁶⁴. However, when these SNPs were examined in Tunisian and Hungarian populations, no association was found, likely due to insufficient study power^{66,74}. Further research by Ealy et al.⁸³ in a German cohort found no link between common variants in BMP2 and BMP4 and otosclerosis, although 4 rare variants – including 2 missense mutations, one large deletion, and one synonymous variant – were exclusively found in affected individuals. Functional assays revealed that the large deletion in BMP2 and the missense mutation p.(Asn150Lys) in BMP4 led to decreased Smad receptor phosphorylation⁸³. Additional studies in an Indian cohort demonstrated elevated levels of BMP2 and BMP4 in otosclerotic stapes tissues, reinforcing the involvement of these proteins in otosclerosis⁶⁴.

TNFRSF11B

The gene *TNFRSF11B* is responsible for coding OPG, which acts as a decoy receptor for the RANKL. Research has highlighted OPG's involvement in otosclerosis, with studies showing reduced OPG mRNA expression in stapes tissue from patients compared to normal tissue⁸.

Alterations in the expression of OPG have been associated with diseases such as osteopetrosis²⁶, osteoporosis²⁷, otosclerosis^{19,28}, juvenile and adult Paget's disease of bone²⁹, and celiac disease characterised by high-turnover osteoporosis³⁰.

In genetic studies focusing on otosclerosis, a SNP in *TNFRSF11B*, rs1485286, displayed marginal significance in a Belgian-Dutch male population (p value 0.049)⁸².

Meanwhile, analysis of 12 Italian patients from otosclerosis-affected families did not reveal pathological mutations; however, the polymorphism rs2073618 was present in 10 of these patients. Further sequencing of the polymorphism in 98 unrelated patients did not show an association with otosclerosis⁸⁴. However, in an Indian male population, SNP rs2073618 was significantly linked to otosclerosis⁸. Meta-analyses incorporating data from Italian and Indian populations affirmed the association of this SNP with the condition⁸. A subsequent meta-analysis involving Tunisian, Indian, and Italian samples also supported this association⁸⁵.

Role of inflammation and oxidative stress

The molecular profile of the otic capsule is markedly different from other bones in the body, characterised by a down-regulation of proinflammatory cytokines, and an up-regulation of anti-inflammatory cytokines¹⁸, to the point that proinflammatory cytokines in the cochlea are generally considered markers of disease and have been associated with HL, with anatomical communication between the otic capsule and the cochlea perilymph¹⁹, and with pathological new bone formation within the membranous labyrinth (labyrinthitis ossificans)³⁵. TNF α and its receptor were reported to be over-expressed during active otosclerosis⁸⁶, and because TNF α promotes bone resorption, it may act as a potential catalyst for the dysregulation of bone metabolism in otosclerosis, and may also be a potential contributor to the development of SNHL in otosclerosis⁸⁷. Moreover, angiotensin II is a key regulator element for the production of proinflammatory cytokines, it has been reported to be a key factor for inflammation and bone remodelling in otosclerosis, providing a link between the inflammatory and the endocrine pathways in the context of the disease⁸⁸.

Oxidative stress has the potential of impacting several cell signalling pathways, and it has been linked to other forms of HL. In otosclerotic patients, immunohistochemical studies have demonstrated an increase in 4-hydroxynonenal (HNE)-protein adducts in comparison with controls. 4-HNE protein adducts are a major bioactive marker of lipid peroxidation which act also as second messengers of free radicals. Although 4-HNE protein adducts were also present in control samples, the primary difference lies in their distribution: they are confined to the periosteal region in controls, whereas in otosclerotic samples HNE-product positive areas are multifocal and irregular⁸⁹.

Role of the immune system

It has been suggested that the immune system, particularly an autoimmune reaction targeting the otic capsule, might play a significant role in the development of otosclerosis, and is supported by the fact that immune cells and immune-regulatory factors were discovered in the regions impacted by otosclerosis⁸⁷. Initial studies speculated that an autoimmune reaction against type II and other less prevalent collagens could be a potential trigger for the disease⁹⁰. The COL2A1 gene, which codes for type II collagen, was targeted for study because this type is plentiful in the globuli interossei, and it has been linked to localised chondrodysplastic lesions⁹¹. Nonetheless, further research involving genetic studies, histological examinations, and immunohistochemical tests have failed to confirm the hypothesis that an autoimmune reaction to collagen is the leading cause of otosclerosis⁹².

Additionally, it has been postulated that otosclerosis may be significantly influenced by an autoimmune response initiated by persistent infection with measles virus⁸⁷, though definitive proof is still pending.

HLA is an essential part of the human major histocompatibility complex, crucial for presenting antigenic peptides to T cells and controlling the immune response. HLA has been linked to various diseases with an immunologic basis. Although some studies have found associations between certain HLA antigens and otosclerosis, these associations have not been consistent across various studies⁸⁷. Nevertheless, the evidence suggesting a significant relationship between HLA and otosclerosis points to an immunological component in the disease, with certain HLA markers potentially affecting susceptibility within specific populations⁸⁷. Further investigation is needed to confirm any substantial connections between HLA antigens and otosclerosis.

Role of the endocrine system

Oestrogen

Numerous studies have explored the influence of the endocrine system on the development of otosclerosis, particularly given its more frequent occurrence in females and reports of its manifestation or progression during pregnancy. However, the link with pregnancy is still subject to debate. For instance, a retrospective study did not establish a correlation between the number of pregnancies or children and the progression of otosclerosis-induced HL⁹³. Proposed mechanisms include the possibility that variants of the oestrogen receptor might mediate abnormal bone remodelling in response to oestrogen. Furthermore, oestrogen promotes

hyperprolactinaemia, which has been linked to increased bone resorption. This process could counteract the effects of oestrogen itself on bone by diminishing the osteoclast response to RANKL, thereby reducing bone resorption⁹⁴.

Renin-angiotensin-aldosterone (RAA) system

The RAA system regulates blood pressure, but is also involved in bone resorption and formation, and specifically angiotensin II has been implicated in key events of inflammation and bone remodelling by its interaction with various growth factors and cytokines^{88,89}. The hypothesis that the RAA system plays a role in the development of otosclerosis may have been influenced, to some extent, by the observed activation of this pathway during pregnancy⁹⁵, coupled with the notion that otosclerosis often appears during or soon after pregnancy. In a 2008 candidate gene-based association study on a French population, polymorphisms in the angiotensin and angiotensinogen-converting enzyme genes associated with higher plasma concentrations of angiotensin II were associated with an increased relative risk of developing otosclerosis⁵⁵. Moreover, the same study reported that angiotensin II enhances the secretion of interleukin 6 (IL6) and reduces alkaline phosphatase activity in vitro exclusively in otosclerotic cells, indicating that angiotensin II may play a part in disrupting bone remodelling processes, contributing to the onset of otosclerosis⁵⁵. However, these results were not replicated in another candidate gene-based study in a large Belgian-Dutch population⁹⁶, and in a study on a Hungarian population⁶⁶.

Parathyroid hormone (PTH)

PTH is secreted by the parathyroid glands in response to decreased blood calcium levels, stimulating osteoblasts to release RANKL, which in turn increases bone resorption and liberates more free calcium into the blood⁹⁴. Given the significant role that PTH plays in bone metabolism, its involvement in the development of otosclerosis has been suggested. Research has shown that higher concentrations of PTH are necessary to enhance adenylate cyclase activity⁹⁷. Additionally, in otosclerotic stapes cell cultures, there is a decreased expression of PTH-PTH-related peptide receptor mRNA accompanied by a reduced cyclic AMP response⁹⁸. These findings suggest that a dysfunctional response to PTH may contribute to the abnormal bone turnover observed in otosclerosis.

Vitamin D receptor

Vitamin D stimulates intestinal absorption of calcium, which is associated through an increase in calcitonin, with a decrease in bone resorption⁹⁹. Due to their role in bone

metabolism, vitamin D and its receptor were proposed as contributing factors to the development of otosclerosis. Yildirim and colleagues¹⁰⁰ genotyped four polymorphisms of the vitamin D receptor gene in a small Turkish population, and found that 3 (Bsm I-rs1544410, Apa I-rs7975232, and Taq I-rs731236) were associated with otosclerosis. However, these results have not yet been replicated in a larger cohort, and therefore it is not possible to draw conclusions on the possible role of vitamin D receptor in the pathophysiology of otosclerosis.

Measles virus

Over the past 30 years, many authors investigated the potential role of measles virus in the development of otosclerosis. The first account of this theory was published in 1986 by McKenna and colleagues¹⁰¹ who identified filamentous structures resembling measles virus nucleocapsid in osteoblast-like cells in otospongiotic tissue specimens. Over the years, several techniques have been used to investigate this association, including electron microscopy, immunohistochemistry, perilymph analysis, reverse transcription polymerase chain reaction (RT-PCR), reverse transcription-quantitative polymerase chain reaction (RT-QPCR), and glyceraldehyde 3-phosphate (GADP) to detect mRNA of measles virus in otosclerotic stapes and control samples¹⁰²⁻¹⁰⁵. However, other studies could not find evidence of measles virus or of a reaction to it in otosclerotic samples^{106,107}. The organotropism demonstrated by the measles virus for the otic capsule in humans and primates is due to the complementary cell surface structures CD46 and CD150, which act as virus receptors^{108,109}. Some studies showed the existence of novel splice variants of CD46 present exclusively in otosclerotic stapes footplates¹¹⁰⁻¹¹². An unresolved question lies in the temporality of this relationship: does measles virus trigger the production of new CD46 splicing variants, or do pre-existing unique isoforms enhance virus affinity and facilitate virus replication? The solution might be found in the activity of various regulatory proteins for alternative splicing, which result in distinct expression patterns and modified functions of CD46. In a study by Schrauwen and colleagues⁸², 2 (rs2796267 and rs2796270) out of 7 SNPs in CD46 were significantly associated with otosclerosis in males of Belgian-Dutch origin, but the results were not replicated in a French population analysed in the same study. However, the exact role of measles virus in the pathogenesis of otosclerosis and the contribution of genetic factors to this process remain to be described.

Genome wide association studies

One of the limitations of association studies lies in the fact that candidate genes to be tested must be selected in advance based on their potential role in the pathophysiology of otosclerosis. Different from association studies, GWAS is free from the need of hypotheses formulated in advance, and can therefore identify genes associated with the disease that had not been previously considered. GWAS aim to identify association between genetic variants and specific phenotypes (in this case, clinical otosclerosis) by surveying the genome of individuals affected by the disease and controls, and looking for genomic variants that occur more frequently in cases than in controls.

The first GWAS was published in 2009 by Schrauwen and colleagues¹¹³, performed in a population of 1,149 Belgian, Dutch, and French patients and 1,174 matched controls, and identified two regions on chr7q22.1 and chr11q13.1 associated with otosclerosis. The chr7q22.1 region is located near the *RELN* gene and harbours an intronic SNP rs3914132 found to be strongly associated with the disease. In the same study, a notable correlation with otosclerosis was identified for the SNP rs670358 located on chromosome 11q13.1, a finding that was later confirmed in two separate subpopulations. Additionally, another SNP in this region, rs494252, showed a significant link to otosclerosis in a work by a Tunisian group¹¹⁴. This SNP is positioned intronically within the *CDC42BPG* gene and close to *EHD1* and *MEN1* genes. Both *EHD1* and *MEN1* are known to be important in the development of bone and cartilage^{115,116}. However, no subsequent research has definitively shown that these genes play a role in the pathogenesis of otosclerosis.

In 2023, Rämö and colleagues⁶⁷ published the largest meta-analysis of GWAS on otosclerosis, utilising data from 3 population-based biobanks that comprised 3,504 cases and 861,198 controls. This study identified 27 risk loci, 23 of which were new, and confirmed associations with otosclerosis for the *RELN* gene and 3 previously reported candidate genes or linkage regions: *TGFβ1*, *MEPE*, and *OTSC7*. Most of the loci identified were situated near protein-coding genes that are implicated in bone remodelling and mineralisation, which are already associated with severe skeletal disorders such as diaphyseal dysplasia (*TGFβ1*) and osteopetrosis (*CLCN7*, *TNFSF11*).

RELN

The region chr7q22.1, which includes an intronic SNP rs3914132 within the *RELN* gene, has been consistently identified as having a strong link with otosclerosis, from

the first GWAS¹¹³ to subsequent studies across diverse populations^{114,117-120}. However, some studies lacked sufficient power to reliably detect this association^{66,119}. Priyadarshi et al.¹¹⁷ conducted a meta-analysis using a cumulative population from multiple studies, comprising 2,670 cases and 2,812 controls, and reported a significant association of the rs3914132 polymorphism with otosclerosis across different populations and genetic models.

The *RELN* gene, responsible for producing the reelin protein, plays a crucial role in neural migration and positioning in the developing brain. Reelin is produced exclusively by neural tissues and is implicated in the development of several neurological disorders¹²¹. Disruptions in reelin signaling have been reported in diseases such as bipolar disorder, schizophrenia, and autism¹²²⁻¹²⁴.

The role of reelin in bone metabolism remains largely unclear. However, research by Dou and colleagues¹²⁵ on multiple myeloma suggests that reelin significantly influences bone formation and the balance between osteolysis and osteogenesis. High levels of reelin are expressed by osteocytes, the bone's mechanosensing cells¹²⁶, and the protein may contribute to the mechanosensory adaptation mechanism of bone remodelling, as it is detected with elevated expression in limbs compared to skull bones¹²⁷. Moreover, distinct expressions of reelin have been observed in the stapes tissues of humans with otosclerosis¹²⁰, and a recent study demonstrated the role of *RELN* variation in familial ankylosing spondylitis, further strengthening the role of this gene in disorders of bone remodelling¹²⁸. However, the exact mechanism of *RELN* in the pathogenesis of otosclerosis remains unclear.

Next generation sequencing

By massive parallel DNA sequencing (sequencing millions of fragments simultaneously per run), NGS allows a high-throughput sequencing of the complete genome, the exome (meaning all coding regions), or selected custom-panels of genes. By being relatively fast and cost-effective, this approach has broken down the limitations associated with sequencing only targeted genes, and has allowed the identification of new genes involved in the pathogenesis of otosclerosis: *SERPINF1*, *ACAN*, and *MEPE*.

SERPINF1

In 2016, Ziff and colleagues¹²⁹ identified multiple missense mutations in the serpin peptidase inhibitor-clade F (*SERPINF1*) gene using various genetic techniques, including whole exome sequencing (WES), on 4 families that exhibited an autosomal dominant inheritance pattern of oto-

sclerosis. *SERPINF1* encodes pigment epithelium-derived growth factor (PEDF), a potent angiogenesis inhibitor and a known regulator of bone remodelling. Angiogenesis is a key feature of otosclerosis, and is associated with both Schwartze's sign and the increased promontory blood flow observed in Doppler flowmetry¹³⁰. Moreover, mutations in *SERPINF1* are linked to the rare type 4 osteogenesis imperfecta, another bone remodelling disorder¹³¹. However, a larger study conducted in 2019 by Valgaeren et al.¹³² on 1,604 unrelated patients, 62 probands from large families, and 1,538 controls, only found 3 missense variants previously reported by Ziff et al.¹²⁹ (c.167C > G, c.331G > A, c.392C > A) in 5 patients and 4 controls. Familial analysis identified 12 variants in all affected family members; however, these variants were also frequently found in the control population, which complicates establishing a pathogenic role. None of the variants reported by Ziff and colleagues¹²⁹ were found in any of the 62 large families studied. Additionally, a study by Richard et al.⁷⁸ in 2015 using proteomic analysis and immunostaining found decreased expression of *SERPINF1*-012 in otosclerosis patients, with or without *SERPINF1* mutations; however, these results have not been replicated.

ACAN

The *ACAN* gene, located at the *OTSC1* locus, encodes aggrecan, the primary non-collagenous component of the cartilaginous extracellular matrix, which is essential for cartilage function and skeletal development³⁸. The potential role of *ACAN* in otosclerosis was first suggested by Dawson in 2018 at the Molecular Biology of Hearing and Deafness meeting. He reported the findings from 19 probands from large otosclerosis families who were tested using WES, followed by targeted NGS of 61 candidate genes in 160 familial otosclerosis patients. Notably, more than 20% of these patients carried rare variants of the *ACAN* gene. In a subsequent study in 2021, Højland and colleagues¹³³ sequenced the entire *ACAN* gene – including all coding regions, exon-intron boundaries, and untranslated regions (UTRs) – in 1,468 unrelated patients, 29 familial cases, and 1,437 unscreened controls. This study identified 14 nonsense and missense variants. *ACAN* is distinguished by a remarkable spectrum of variants in terms of number, effect size, allele frequency, and direction of effect. Specifically, some variants showed strong effects but low frequency, resembling the transmission pattern of monogenic diseases, while others had minimal effect sizes and were more common, serving as susceptibility factors.

MEPE

The *MEPE* gene encodes a matrix extracellular phosphoglycoprotein with a role in bone homeostasis, suppression of renal calcification, and regulation of serum phosphate. In a study on a large Turkish family affected by hereditary congenital facial paresis and a mixed form of HL similar to otosclerosis, a mutation of the *MEPE* gene segregating with the phenotype was reported¹³⁴. To confirm this finding, a large case-control study was performed, including 123 members from 62 families, 1,604 cases, and 1,538 controls. This study identified 6 heterozygous frameshift and nonsense variants in 19 patients and 3 unscreened controls, indicating a relatively low frequency of these variants in the population but a high effect size. These results were replicated in the large GWAS meta-analysis by Rämö et al.⁶⁷, which also reported the dynamic changes in *MEPE* expression throughout postnatal development in the murine inner ear by immunostaining, going from a more diffused expression at 2 days of life to a limited expression to mature osteocytes at 3 months of age.

Conclusions

Overall, the hereditary pattern in otosclerosis is predominantly complex, involving both environmental and genetic factors, a model already described for other relatively common diseases such as age-related HL and coronary artery and Alzheimer's disease. Unlike other genetic disorders, where linkage analysis, positional cloning, and GWAS have led to the identification of many causative genes, the genetics of otosclerosis remain largely unidentified. Linkage analysis of monogenic forms of otosclerosis has led to the identification of 9 loci, but the genes responsible and their variants have yet to be extensively described. So far, the most promising results have come from GWAS, which identified strong associations with novel candidate regions. The use of NGS to zoom into these candidate genes in search of causative variants has recently led to the identification of large-effect risk factors in *MEPE*¹³⁴ and variants with high variation in frequency and effect size in *ACAN*¹³³, highlighting the potential of this approach.

Apart from genetic studies, epigenetic analyses could provide valuable insights into the pathophysiology of otosclerosis by correlating the impact of environmental factors on local gene expression, as has been described in numerous other complex diseases. A limitation of this approach is the need to use samples of stapes tissue, in contrast with genetic studies that mainly use DNA drawn from blood samples. Additionally, future studies should include clinical data,

especially audiometric testing and temporal bone imaging, for better correlation with genetics and pathophysiology, as most large databases have not included such information. An integrated approach, utilising various genetic and epigenetic techniques in conjunction with clinical data and possibly aided by new bioinformatic techniques, will likely provide a better understanding of the pathophysiology of otosclerosis.

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

SC, FL, LB: conceived the initial idea for the narrative review and developed the structure of the article; GF, FF: performed the literature review and critically analyzed the sources. All authors contributed significantly to drafting the manuscript, revising it for important intellectual content, and approving the final version to be submitted. Each author has read and agreed to the published version of the manuscript.

Ethical consideration

Not applicable.

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Current trends in imaging for otosclerosis and the potential role of photon-counting computed tomography

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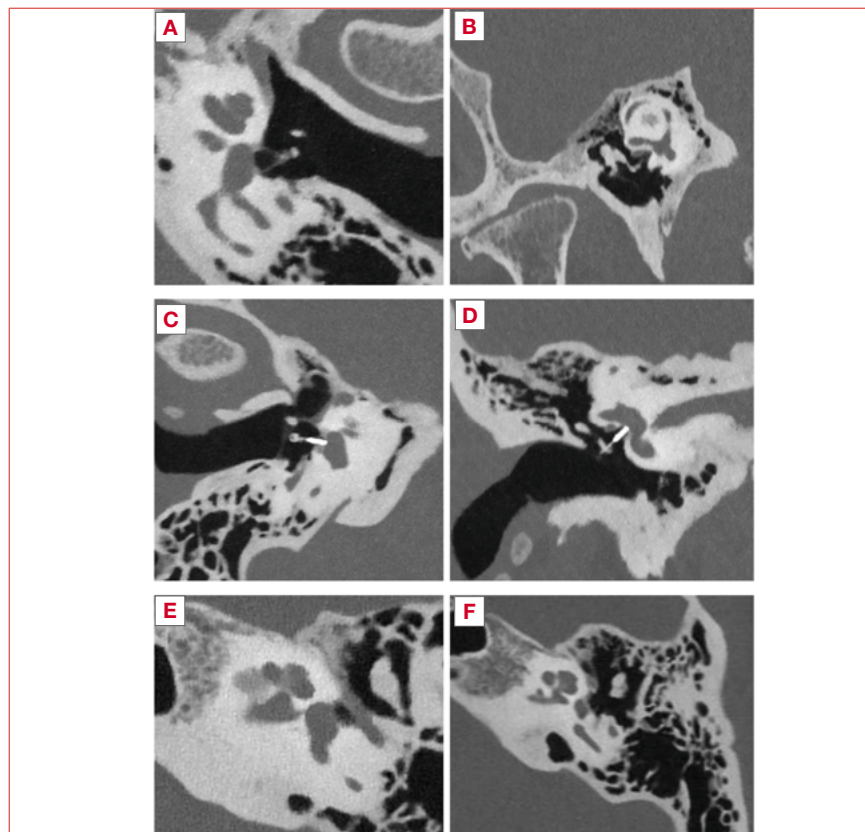
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Cover figure. Photon counting detector CT acquisition: A and B show the normal anatomy of a healthy ear; C and D show the accuracy in stapedial prosthesis positioning evaluation; E shows a focal demineralisation of the anterior portion of internal auditory canal; F shows a diverticulum.

Summary

Otosclerosis is a primary otodystrophy that impacts the osseous architecture of the otic capsule within the temporal bone, resulting in progressive hearing loss. High-resolution computed tomography (HRCT) has traditionally been the gold standard imaging modality in otosclerosis, providing critical information in both diagnosis and surgical planning. However, its sensitivity varies widely. Recent advancements in imaging technology, such as ultra-high-resolution CT (UHRCT), provide higher spatial resolution and lower doses of radiation but, especially if based on cone beam CT (CBCT), face challenges in standardising bone density and are often limited by beam-hardening artefacts in the presence of metallic prostheses. Photon-counting detector CT (PCDCT) represents a promising UHRCT technology that directly converts photons into electrical signals, enhancing dose efficiency and image quality while reducing beam-hardening artefacts. Initial findings seem to indicate that PCDCT offers superior visualisation of otosclerotic foci and prosthesis positioning compared to traditional HRCT. Furthermore, PCDCT allows for less radiation exposure. This review

examines the roles that HRCT and UHRCT, based both on CBCT and PCDCT, as well as magnetic resonance imaging, currently have in the imaging evaluation of otosclerosis. The findings highlight that while HRCT remains the standard, UHRCT and particularly PCDCT significantly improve the assessment capabilities, overcoming many limitations of previous technologies. Incorporating PCDCT imaging into routine clinical practice could lead to more precise diagnosis of otosclerosis, better surgical planning, and improved patient outcomes, ultimately granting more tailored and effective treatment strategies for otosclerosis, in line with the goals of precision medicine to optimise patient care.

Key words: otosclerosis, high resolution computed tomography, ultra-high resolution computed tomography, cone beam computed tomography, photon counting detector computed tomography, magnetic resonance imaging

Introduction

Otosclerosis is a primary otodystrophy that affects the osseous architecture of the otic capsule within the temporal bone¹. The primary symptom of the disease is progressive hearing loss (HL), which can be conductive or mixed and only rarely purely sensorineural^{2,3}. Hearing impairment is commonly bilateral, but can also occur unilaterally. Tympanometry typically reveals a good middle ear ventilation by a type A tympanogram, although stapedial reflexes are often absent or, exceptionally, exhibit a two-staged pattern (on-off stapedial reflexes). Tinnitus and vestibular symptoms may or may not accompany the HL². While otoscopy is usually negative, rare cases may present with Schwartz's sign, a localised red blushing on the promontory attributed to hypervascularised otosclerotic lesions⁴.

Histological manifestations of otosclerosis have been recognised for over a century. However, it is only in the last 25 years that different imaging techniques have become useful in the evaluation of this condition. Even though imaging is not imperative for diagnosis of otosclerosis^{5,6}, advancements in radiologic techniques have significantly increased the importance of imaging in both diagnosis and therapeutic decision-making⁷⁻¹⁰.

In current clinical practice, high-resolution computed tomography (HRCT) represents the examination of choice for radiologic assessment of patients with otosclerosis, both in the pre- and postoperative phases (e.g., in the event of complications or when surgical revision is necessary)⁷⁻¹⁰. Despite the several potential applications of HRCT in the evaluation of a patient with symptoms of otosclerosis, specific criteria for its use have not been clearly defined in the literature¹¹. Moreover, other imaging modalities, such as magnetic resonance imaging (MRI)^{12,13} or even densitometry^{14,15}, can play a role in assessing specific aspects of this disease.

This review examines the current state of the art in imaging for otosclerosis, discussing the importance for clinical applications. Furthermore, it focuses on the impact of new technological improvements on diagnosing, planning treatment, and enhancing patient outcomes, also reporting

on experience with the novel photon counting detector CT (PCDCT) technology in otosclerosis evaluation.

High-resolution computed tomography

HRCT involves acquiring images (thickness mostly 0.6 mm) with a high spatial frequency reconstruction algorithm to evaluate and characterise various conditions affecting different organs, particularly the petrous bone. HRCT is commonly conducted using multidetector CT (MDCT) scanners, which can acquire near-isotropic data.

HRCT is currently the most used imaging technique for pre- and postoperative assessment of otosclerosis and is widely considered the gold standard in imaging evaluation of this condition^{5,16-20}. It provides clinicians with crucial information for making therapeutic decisions, especially in atypical or ambiguous clinical presentations, and plays a pivotal role in enabling differential diagnosis.

Radiologically, otosclerosis is categorised into 2 types: fenestral and retro-fenestral. Generally, cochlear forms are preceded by the fenestral form, leading some authors to consider them as a pathologic continuum^{5,21}. Fenestral otosclerosis accounts for 70-80% of cases, primarily presenting as pure form rather than the rarer retro-fenestral form^{1,22,23}.

Through cross-sectional X-rays, HRCT can effectively highlight both the otospongiotic and sclerotic phases of otosclerosis. Otospongiotic foci appears as hypodense regions with decalcification within the otic capsule^{22,24,25}. False negatives can be correlated with small lesions or those in sclerotic stages characterised by attenuation similar to adjacent normal bone⁷.

Specifically, in the fenestral form of otosclerosis, bone remodelling foci typically localise along the medial tympanic cavity wall, predominantly at the level of the fissula ante fenestram, and occasionally extending to the promontory or round window (Fig. 1A). Less frequently, foci may be observed in the tympanic segment of the facial bony canal¹⁰. Advanced fenestral otosclerosis may exhibit complete thickening of the entire platina. Retro-fenestral otosclerosis, on HRCT, often shows variably dense areas throughout the petrous bone. Notably, the cochlea may display a char-

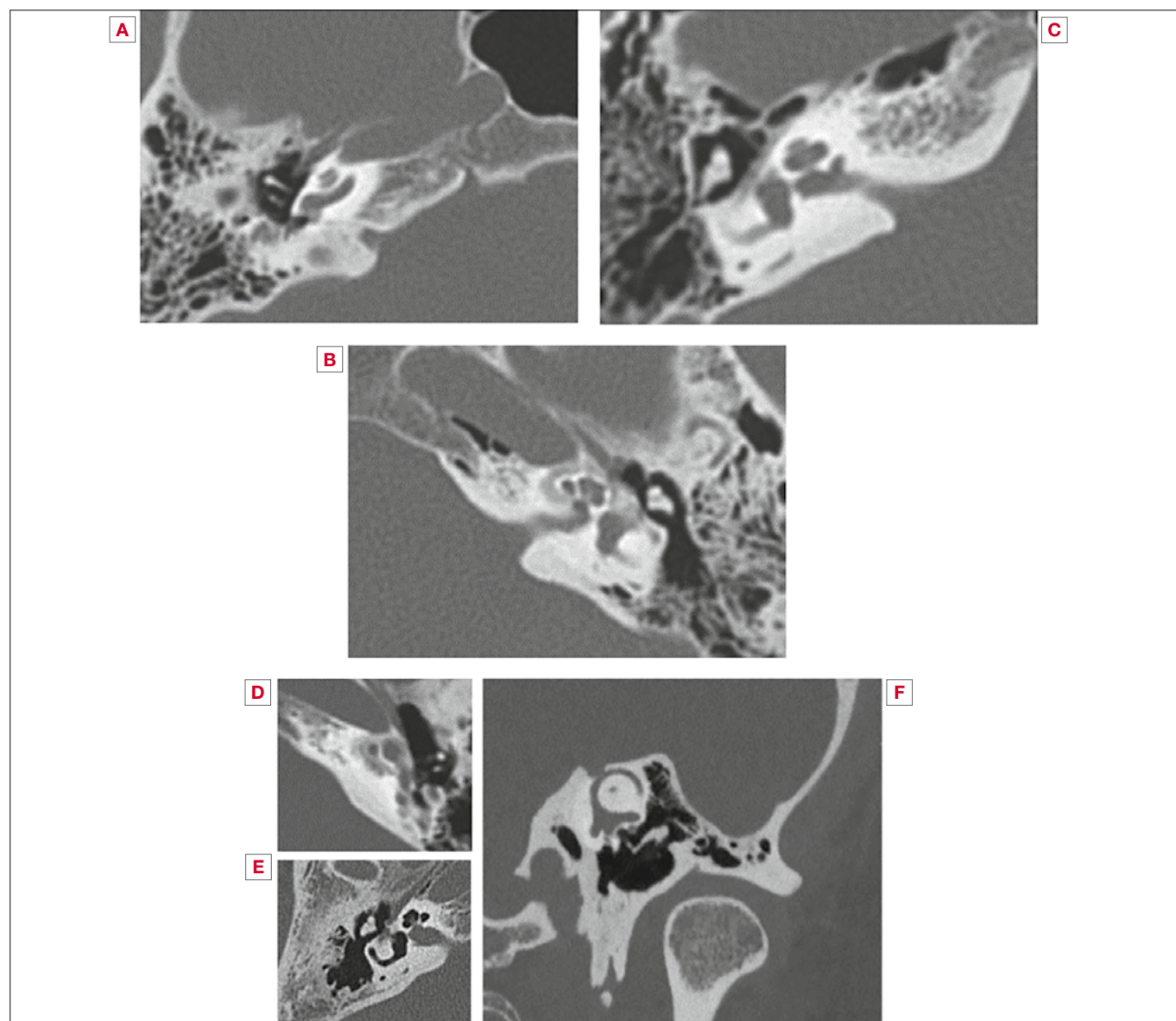


Figure 1. Computed tomography pictures in otosclerosis. **A)** Otosclerotic focus localised at the level of fissula ante fenestram of a right ear; **B)** Valvassori's sign: double ring appearance of otic capsule in a retrofenestral form of otosclerosis of a left ear; **C)** Internal auditory canal diverticulum on a right ear; **D)** Right ear pneumolabyrinth; **E)** A complete subversion of the otic capsule in an advanced otosclerosis in a left ear; **F)** Superior semicircular canal dehiscence from the dilatation of the superior petrosal sinus in a left ear.

acteristic double-ring appearance known as the Valvassori's sign (Fig. 1B), and additional involvement of other labyrinthine structures, the facial canal, or the internal auditory canal are commonly observed.

One of the characteristic lesions associated with otosclerosis involving the internal auditory canal (IAC) is the diverticulum, which manifests as an erosion in the anterior canal wall and is considered a form of "cavitary otosclerosis"

26-28. It is thought to be present in the 70% of the otosclerotic petrous bone with IAC involvement 29. As well as with HRCT, its presence has been described in post-mortem otopathological studies 29. However, IAC diverticula have been documented in patients lacking radiographic evidence of fenestral or retro-fenestral otosclerosis and even in histologically normal temporal bones from individuals with normal hearing 26,29 (Fig. 1C).

A study conducted by Wells and colleagues²⁶ on 97 petrous bones studied with both HRCT and histopathologic section demonstrated that, while not pathognomonic, IAC diverticula are frequently observed in cases of otosclerosis, particularly when they are sizable. Similar results were reported in the study by Wang and coworkers³⁰. A study by Pippin and colleagues³¹ examining 807 petrous bone HRCT scans revealed that the presence of diverticula correlated with HL, regardless of whether otosclerosis signs were present. Intriguingly, sensorineural HL (SNHL) showed a higher association with IAC diverticulum compared to traditional conductive or mixed findings of otosclerosis, both in petrous bones with or without other radiological signs of otosclerosis. This association was not confirmed by the latter study of Burd and colleagues³², who concluded that there are no clear audiometric implications in the presence and even the morphology of IAC diverticula.

According to the study by Yagi and colleagues¹⁸, otosclerotic foci are distributed in the anterior portion of the oval window (essentially at the level of the fissula ante fenestram) in more than 95% of cases in their cohort, in the anterior segment of the IAC (often defining the diverticulum) in 46.8%, and in the pericochlear area in 26%.

Another aspect to be evaluated with HRCT is the thickness of the otic capsule contour and the anterolateral to the anterior margin of the oval window. Sanghan and colleagues³³ hypothesised and demonstrated that individuals with otosclerosis exhibit a measurable increase in otic capsule thickness adjacent to the anterolateral aspect of the anterior margin of the oval window on CT compared to individuals with normal hearing.

The link between radiologic findings and audiometric results in otosclerosis has been explored by many authors, although there is still not a clear consensus regarding this relationship. Mangia and coworkers³⁴, evaluating the imaging and audiometric findings of 40 ears with surgically confirmed otosclerosis, found that ears with endosteal extension of the foci or with multiple affected sites within the otic capsule had worse bone-conduction hearing thresholds, and that mixed fenestral and retro-fenestral disease was associated with higher pure tone audiometric values. On the other hand, Zanini et al.³⁵ found no significant correlation between the location of otospongiotic foci and air conduction, bone conduction, or air-bone gap, disconfirming the thesis by Mangia et al.³⁴. Intriguingly, the otospongiotic involvement of the round window, especially if it is fully obliterated, is reported to be associated with worse bone thresholds both in the pre- and postoperative periods^{36,37}. Various grading systems for otosclerosis have been devel-

oped based on HRCT findings, but none have gained wide acceptance. For example, Rotteveel et al.³⁸ introduced a system classifying otosclerosis into fenestral and retro-fenestral subtypes.

However, the sensitivity of HRCT in detecting otosclerosis varies across studies. In a systematic review on HRCT sensitivity conducted by Wegner and colleagues⁶, based on 7 studies of moderate to high relevance and moderate to low risk of bias, reported sensitivities ranged from 60% to 95%, with high specificity that was 100% in two studies. Moreover, these authors demonstrated that the positive predictive value (PPV) of HRCT was particularly high in cohorts with a high prevalence of the disease, and that diagnostic performance was better in more recent studies, possibly due to technological advancements. Similarly, in another systematic review, Kanzara and Virk¹⁹ reported that HRCT had a sensitivity of 58%, and was also associated with high specificity (95%) and PPV (92%).

The wide variation of the sensitivity of HRCT reported in the literature may be related to differences in image quality, slice thickness, and study protocols, as well as radiologist experience in petrous bone imaging^{39,40}. From these findings, it clearly emerges that adequate study quality and protocol, as well as dedicated radiologists, should be advised¹⁷.

Preoperative HRCT evaluation

In preoperative evaluation with HRCT for stapedial surgery, several factors need to be considered. Firstly, the size of the oval window niche, potentially reduced by osseous hypertrophy, congenital anomalies, or otosclerotic foci, requires precise assessment since it can impact postoperative results. Ukkola-Pons et al.⁴¹ established a minimal normative value of 1.4 mm for the niche height, below which the risk of surgical difficulties increases. Additionally, the potential obliteration of the round window by otosclerotic foci demands careful consideration as it can negatively affect post-surgical outcomes^{21,24,42,43}. Extensive damage to the otic capsule and inner hearing canal must also be evaluated⁴².

The relationship between the facial nerve and the oval window, particularly in cases of prolapse or dehiscence, necessitates careful assessment due to its significant impact on surgical feasibility, as does the presence of a very high jugular bulb. Integrating preoperative assessments with HRCT into the clinical workflow can enhance the surgeon's ability to anticipate and assess potential intraoperative challenges and estimate outcomes more accurately⁷.

Another relevant aspect is the concomitant presence of otosclerosis and superior canal dehiscence. Superior canal dehiscence can present with variable symptoms including vertigo triggered by sound pressure or head movement, autophony, conductive hyperacusis, pulsatile tinnitus, and conductive HL⁴⁴. Given the importance of appropriate differential diagnosis between the 2 conditions joined by the presence of conductive HL, some authors have reported that outcomes of stapes surgery in patients with concurrent superior canal dehiscence syndrome and otosclerosis are not straightforward concerning the probability of successful surgery in this particular group of patients^{45,46}. A recent systematic review concluded that although the length and location of the dehiscence might inform surgical decisions, it is not possible to draw definitive conclusions about the appropriate indications for surgical treatment due to the limited number of cases with adequate data reported in the literature⁴⁷.

Preoperative HRCT assessment can also rule out conditions that can mimic otosclerosis, such as specific inner ear malformations (IEM) or ossicular chain issues. Incomplete partition types II and III, as well as some forms of cochlear hypoplasia (mostly types II, III, and IV), can be associated with mixed or pure conductive HL, type A tympanogram, and lack of stapedial reflexes due to increased endolymph pressure or congenital alterations of articulation between the stapes and oval window⁴⁸. An interruption of the ossicular chain occurring laterally from the stapedial muscle insertion can also be associated with conductive HL, normal tympanogram, and absent stapedial reflexes.

Postoperative HRCT assessment of otosclerosis

In cases of suboptimal outcomes following stapes surgery or when a patient experiences hearing deterioration over time, an imaging study is advisable. In such cases, HRCT can evaluate the placement of the stapedial prosthesis and any potential dislocation. Additionally, HRCT can assess other possible issues such as erosion of the long process of the incus – a frequent cause of stapedial prosthesis dislocation – or the presence of granulation tissue, a perilymphatic fistula, or a pneumolabyrinth (Fig. 1D).

If preoperative HRCT was not conducted, imaging can also reveal unexpected conditions that may have limited the surgical outcome, such as round window obliteration⁴⁹ or a concomitant and previously undiagnosed superior semicircular canal dehiscence^{45,50}. Rarely, in cases of long-term hearing deterioration, HRCT can reveal progression of

the disease with a complete subversion of the otic capsule (Fig. 1E)⁵¹.

HRCT has also been used to check the postoperative positioning of stapes prostheses and correlate intravestibular protrusion with surgical outcomes. The criteria for measuring intravestibular protrusion of the prosthesis vary among different studies, as does the measure of insertion considered normal. Williams and Ayache⁵² set the limit at 1 mm, Rangheard et al.⁵³ at 2 mm, and Whetstone et al.⁴⁹ at 50% of the vestibule width. Meanwhile, the depth of non-metallic prosthesis tips in the vestibule is thought to be generally underestimated⁵⁴, and depth insertion of metal prostheses tends to be overestimated due to beam hardening artifacts caused by the metal⁵⁴⁻⁵⁶. Because of the inhomogeneous criteria, as well as the technical difficulties due to low spatial resolution and the predisposition to artefacts, in general, HRCT is yet not considered as a reliable method for the evaluation of intravestibular protrusion of stapes prostheses^{55,56}.

Is pre- or postoperative imaging assessment necessary?

Given the frequency of a clear clinical appearance of otosclerosis, the use of preoperative assessment with CT can be questioned. As previously discussed, the sensitivity of HRCT can be suboptimal, and it is economically and dosimetrically costly. However, pre- and postoperative CT highlight information for surgical planning and identify concomitant or concurrent conditions that may limit or have limited surgical outcomes, providing the surgeon with greater knowledge of potential surgical difficulties or suboptimal outcomes and giving the patient the best chance of an uneventful surgery. This aspect justifies the suggestion of implementing HRCT whenever otosclerosis is associated with atypical symptoms such as autophony, imbalance, vertigo, oscillopsia, hyperacusis, and aural fullness¹¹.

From a national survey carried out in the US in 2022, 35.3% of surgeons reported routine use of CT, with a significant difference between academic and private practice respondents, especially focusing on patients with vestibular complaints, childhood HL, possible advanced otosclerosis, or any atypical symptoms⁵⁷.

In his systematic review, Wegner⁶ reported that CT might not be essential to confirm otosclerosis in patients with a high clinical suspicion based on conductive HL. Instead, its utility might be better realised in evaluating the extent of the disease or planning surgical interventions rather than serving as a primary diagnostic tool.

In our opinion, a proactive strategy utilising an imaging evaluation, especially in patients with atypical presentations of otosclerosis, can enhance precision in counselling, and in anticipating surgical outcomes and functional results. By adopting a comprehensive preoperative evaluation, even with the best achievable imaging, it is more likely to achieve improved surgical efficiency and decrease intra-operative risks.

Ultra-high-resolution CT

The advent of ultra-high-resolution CT (UHRCT) represents a significant step forward in imaging technologies. This advancement is primarily driven by the introduction of more sophisticated detector systems, such as enhanced ultra-small multi-slice detectors, flat-panel detectors, or the new photon-counting technology detectors, which allow for the capture of images at finer slice thicknesses compared to traditional HRCT. These advanced detectors ensure a higher matrix size during image reconstruction, resulting in clearer and more detailed images, and facilitating better visualisation of minute anatomical structures and pathologies. Given that the slice thickness of conventional HRCT is typically 0.6 mm, this level of spatial resolution may be inadequate for accurately delineating otosclerotic foci smaller than 1 mm^{8,40}. This limitation underlines the need for more advanced imaging techniques that are capable of capturing finer details. In this context, Akazawa and colleagues⁵⁸ analysed the performance of UHRCT based on ultra-small multi-slice detectors. They measured the thickness of the stapes footplate in patients with otosclerosis finding a significant increase in thickness in otosclerosis patients compared to control subjects (0.60 ± 0.09 mm vs 0.46 ± 0.04 mm; $p < .001$). Furthermore, the thickness at the midpoint, where the interobserver variability was lowest, correlated well with surgical difficulty during stapedotomy.

UHRCT with cone beam CT technology

Cone beam CT (CBCT) has become increasingly popular for temporal bone imaging due to its capacity to generate high-spatial-resolution images with low radiation doses^{59,60}. It is mainly based on the emission of a cone-shaped radiant beam (not fan-shaped as in conventional CT) and a solid detector that can be shaped into a large surface panel (flat panel).

The slice thickness of CBCT can range from 0.075 to 0.5 mm⁶¹. However, a significant challenge in using CBCT for bone density assessment is the technical variability in

pixel values. Compared to standard multidetector CT, CBCT is more prone to produce regional artefacts. These artefacts are primarily due to off-axis X-ray beam projections, beam hardening, and scatter radiation. They are especially problematic when high-density materials are present within the beam path but outside the reconstructed field of view, producing very intrusive beam-hardening artefacts⁶², such as in postoperative metallic stapedial prosthesis positioning evaluation. In their prospective study, Redfors et al.⁶³ compared the diagnostic capabilities of CBCT and HRCT in patients with otosclerosis who underwent stapedectomy 30 years prior. The authors found that CBCT is an effective and reliable imaging technique to detect hypodense otosclerotic lesions in the otic capsule, and was comparable to HRCT. On the other hand, Liktors et al.⁶⁴ reported that while CBCT exhibits high sensitivity for histologically confirmed active fenestral otosclerosis, it is significantly less effective at detecting retro-fenestral lesions. In another study by the same group, CBCT was found to be effective in detecting active otosclerosis with a sensitivity of 100%, but its sensitivity dropped to 0% for inactive otosclerosis. Furthermore, CBCT did not have the ability to detect retro-fenestral lesions, marking a significant limitation compared to HRCT. The general sensitivity of CBCT was 61.3% for all cases of otosclerosis, which was less than the sensitivity shown by traditional HRCT⁶⁵. Only recently, in their retrospective case-control study, Deng and colleagues⁶⁶, calibrating CBCT pixel values using 3 internal references to obtain a relative attenuation ratio that allows quantitative assessment of bone density, reported a high sensitivity (97.3%) and specificity (97.1%) of CBCT to diagnose otosclerosis. Another recent study by Xu and colleagues⁶⁷ evaluated the diagnostic capabilities of cone beam based UHRCT and standard HRCT in detecting isolated fenestral otosclerosis. UHRCT showed a sensitivity of 100% when images were evaluated by dedicated neuroradiologists and 87.5% if evaluated by general radiologists, while traditional HRCT demonstrated lower sensitivities, which was 89.2% for neuroradiologists and 41.5% for general radiologists. Significant differences in sensitivity between UHRCT and HRCT were reported, with UHRCT proving more effective in detecting smaller foci under 1 mm. However, the limitations of CBCT in standardising bone density and the subsequent difficulties in evaluating retro-fenestral otosclerotic lesions, as well as the noticeable impact in evaluating prosthesis positioning given by beam hardening artefacts, make this UHRCT study suboptimal for otosclerosis imaging evaluation.

UHRCT with photon-counting detector CT technology

On the other hand, photon-counting detector CT (PCDCT) is an emerging technology with promising results in improving clinical imaging^{68,69}. It directly converts photons into an electric signal, thereby recording each individual photon, allowing for more dose-efficient and high-spatial-resolution imaging^{70,71}. Additionally, PCDCT assigns uniform weighting to each detected photon regardless of its energy level, enhancing the signal-to-noise ratio and reducing beam-hardening artefacts, thereby improving overall image quality^{72,73}. Furthermore, Zhou et al.⁷⁴ demonstrated in a previous cadaver study that PCDCT allows for approximately a 50% dose reduction in radiation.

In a further study by Benson and colleagues⁷⁵, 13 patients underwent temporal bone imaging with both traditional HRCT and UHRCT with PCDCT. Their findings clearly reported that PCDCT provides higher resolution images and requires lower radiation doses compared to traditional HRCT.

As far as we know, no studies on the performance of PCDCT in otosclerosis evaluation have yet been published. Herein, we report a recent experience with PCDCT in the pre- and postoperative evaluation of 6 patients with otosclerosis using a dual-source CT scanner Photon Counting Naetom Alpha (Siemens-Healthineers): 140 kV, mean volume CT dose index = 27.17 [SD, 1.4] mGy, pitch = 0.55, rotation time = 1 second using the high-resolution mode (120 x 0.2 mm collimation) with a dedicated sharp Hr 92 kernel and the smallest section thickness of impressive 0.2 mm.

The Cover figure illustrates the high quality of image acquisition, displaying a detailed representation of the foci as well as all the anatomical structures critical for surgical planning, addressing the limitations of UHRCT based on CBCT reported earlier. However, our current sample size is too limited to reliably assess the specificity and sensitivity of this method in evaluating otosclerosis.

The main advantages of executing an UHRCT with PCDCT are:

- the ease of detection and characterisation of foci's extension due to the very high spatial resolution and standardised density value;
- the precision in the evaluation of stapedial prosthesis positioning due to the absolute reduction of beam hardening artefacts;
- a reduction of the dose vs. traditional HRCT.

Some of the most interesting findings to be anecdotally reported were:

- a typical extension of the classical fissular otospongiotic area in a caudal and rostral direction with involvement of the lateral wall of the vestibule;
- an impressive rate of association between superior semicircular canal dehiscence in patients with otosclerosis, mainly from a dilatation of the superior petrosal sinus, accounting for one third of the evaluated subjects (Fig. 1F);
- the frequent presence of an otospongiotic area in the lateral portion of the anterior wall of the IAC that often hints at a more or less pronounced diverticulum. This finding could support the hypothesis that such a finding is nothing more than a very punctual area of cavitory otosclerosis derived from the evolution of an otospongiotic focus.

It is the authors' opinion that such a promising technique could be considered a game-changer in pre- and postoperative imaging evaluation of otosclerotic patients and could also contribute to a better understanding of the aetiopathologic evolution of otosclerosis.

Magnetic resonance imaging

Although MRI is not the primary imaging modality for evaluating otosclerosis, it can reveal specific changes such as a pericochlear halo of intermediate signal intensity on T1-weighted sequences with pericochlear enhancement in post-contrast sequences^{12,13,21,43}. This enhancement is thought to occur due to the passage of contrast into numerous vessels within the otosclerotic foci²⁵. Occasionally, T2 hyperintensity can also be observed⁷⁶.

Purohit and coworkers⁷⁷ explored the use of MRI as a diagnostic tool for otosclerosis. The study was retrospective, analysing 13 cases from KU Leuven University Hospitals where MRI was used as the primary diagnostic tool instead of HRCT. The findings indicated that MRI could reveal subtle signs of otosclerosis, particularly when specific imaging features like intermediate T1 signal and post-contrast enhancement in perilabyrinthine or pericochlear regions are present. The study concluded that although MRI should not be the first choice for diagnosing otosclerosis, it can effectively detect the condition in patients where otosclerosis was not initially considered. Thus, MRI can lead to more targeted use of HRCT and help confirm the diagnosis.

Moreover, as our group has previously reported^{12,13} the use of MRI 3D-FLAIR sequences before and after gadolinium administration can effectively evaluate cochlear damage caused by the disease. The presence of endocochlear hy-

perintensity and post-contrast enhancement are considered good predictors of permeability changes in the blood-labyrinth barrier. These labyrinthine disturbances might correlate with clinical parameters such as disease duration and the degree of cochlear damage as measured by audiometric thresholds. Our findings represent a significant advancement in understanding the pathogenic mechanisms underlying SNHL in otosclerosis. Specifically, the hyperintensity observed on 3D-FLAIR sequences likely reflects areas of active otospongiotic lesions where increased vascular permeability allows gadolinium to penetrate the cochlear tissues. This hyperintensity can be viewed as a biomarker of active disease, indicating ongoing inflammation and remodelling processes within the cochlea. The correlation between these MRI findings and clinical parameters such as duration of disease and audiometric thresholds supports the hypothesis that these permeability changes contribute directly to the sensorineural component of HL observed in otosclerosis patients.

Our research also provided a possible *in vivo* explanation for the pathogenesis of SNHL in otosclerosis by demonstrating that these imaging findings are not just incidental but are significantly associated with clinical deterioration. By quantifying the extent of cochlear damage through imaging, we can better predict the progression of HL and potentially identify patients who might benefit from early therapeutic interventions aimed at stabilising or reversing these permeability changes. This understanding could lead to more targeted treatment strategies, improving outcomes for patients with otosclerosis.

Additionally, Vicente and colleagues⁷⁸ have explored the use of MRI to monitor clinical treatment responses in otosclerosis. Employing a standard MRI protocol without 3D-FLAIR images, they observed a decrease in enhancement within active bone otospongiotic lesions on T1-weighted post-Gd sequences following drug treatment with sodium alendronate or sodium fluoride. It is proposed that incorporating a 3D-FLAIR sequence with or without gadolinium could be a valuable method to specifically identify active endocochlear damage in patients with otosclerosis, potentially enhancing the effectiveness of drug therapy. Although the efficacy of drug therapy in treating retro-fenestral otosclerosis has not been conclusively demonstrated, this imaging protocol could offer a new endpoint for evaluating the impact of treatment. Finally, when considering cochlear implantation, MRI is helpful for assessing cochlear patency, providing essential insights for surgical planning¹².

Conclusions

HRCT represents the gold standard for imaging evaluation of otosclerosis. Historically, however, it was considered nonessential due to the typically clear clinical presentation and well-defined audiological diagnostic features of otosclerosis, which could often be confirmed intraoperatively. Furthermore, systematic reviews have highlighted the sub-optimal performance of HRCT, primarily due to technical limitations that resulted in limited spatial definition and consequently low sensitivity.

On the other hand, UHRCT and especially PCDCT appear to overcome the limitations of previous imaging modalities in the evaluation of otosclerotic patients. With their extraordinary spatial definition and minimal beam-hardening artefacts in the presence of metallic stapedial prostheses, PCDCT holds great promise to become the imaging modality of choice for otosclerosis both pre- and postoperatively. The advent of PCDCT may lead clinicians to re-evaluate the role of imaging in the clinical management of otosclerosis, especially in the context of precision medicine. Enhanced imaging capabilities may facilitate more accurate diagnosis, better surgical planning, and improved postoperative assessment, ultimately leading to more tailored and effective treatment strategies for patients with otosclerosis.

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

FL: conceptualization, methodology, formal analysis, data curation, writing – original draft preparation; FF, LB, SB: validation; OM: investigation; FL, SDC, FC: data curation; SC: writing – review and editing; SC, SB: visualization; all the authors: supervision and project administration.

All authors have read and agreed to the published version of the manuscript.

Ethical consideration

This study was approved by the Institutional Ethics Committee. Local Review Board do not release acceptance codes for retrospective studies based on clinical practice measures. The research was conducted ethically, with all study procedures being performed in accordance with the

requirements of the World Medical Association's Declaration of Helsinki.

Written informed consent was obtained from each participant/patient for study participation and data publication.

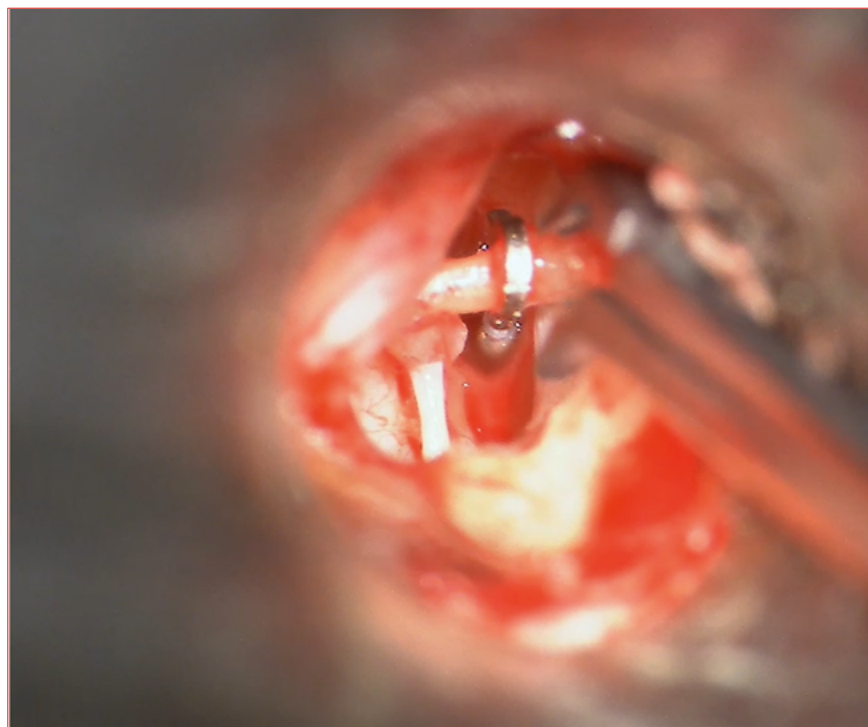
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Update on stapes surgery



Cover figure. Preparing to crimp the stapes prosthesis to the long process of the incus during a stapedotomy procedure.

Summary

Stapes surgery has significantly evolved from the early identification of stapes fixation as a cause of hearing loss in the 18th century to advanced modern techniques. This narrative review examines the historical development and contemporary advancements in stapes surgery, focusing on all the critical aspects of surgical procedures: from patient positioning, to microscopic versus endoscopic visualisation, type of anaesthesia, characteristics of prosthesis, and different surgical techniques. A further analysis of special conditions has been made.

Key words: stapes surgery, otosclerosis, prosthesis, endoscopic surgery, microscope, local anesthesia, general anesthesia

Introduction

The history of stapes surgery is a demonstration that the relentless pursuit of medical innovation has significantly advanced our understanding and treatment of hearing loss (HL). Stapes fixation causing HL was first identified by

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Antonio Maria Valsalva in 1704. In 1841, Toynbee's dissection of 1,659 temporal bones found 39 cases of stapes fixation, linking it to deafness. By 1893, Adam Politzer's histological studies indicated otosclerosis as the cause ¹.

Johannes Kessel described stapes surgery in 1876, attributing HL to increased inner ear fluid pressure. His methods included mobilising or removing the stapes, with mixed success and some risks like labyrinthitis and meningitis ². His techniques were criticised and deemed dangerous by the early 20th century ¹. Surgeons then shifted to "third-window" fenestration techniques, fully established by Jenkins in 1913 with contributions from Lempert, who simplified the procedure ^{3,4}. Samuel Rosen reintroduced stapes mobilisation in the mid-20th century, achieving immediate but often temporary hearing improvement ⁵.

John Shea revolutionised stapes surgery in 1956 by successfully using a Teflon prosthesis to replace the stapes after a complete stapedectomy, with the interposition of autologous material, usually constituted by a vein or perichondrium ⁶. His technique, initially considered dangerous, became standard by the 1960s ⁷. Schuknecht later developed a steel-wire prosthesis in 1960, while Plester proposed a partial footplate removal method, leading to further advancements in stapedectomy procedures ⁸. This advancement paved the way for modern stapes surgery, featuring the use of piston prostheses and the creation of small holes in the footplate. This narrative review aims to provide an overview of the evolution of surgical techniques in stapes surgery, analysing each technical aspect in detail, including the position of the patient during surgery, the instruments used for visualising the middle ear, type of anaesthesia administered, methods

for removing the stapes' superstructure, techniques for creating a hole in the footplate, and the characteristics of the prosthetic piston. Additionally, the review will include a dedicated section on stapes surgery in special conditions.

Surgical procedures

Due to the intrinsic danger of sensorineural hearing damage and the higher rate of complications ^{7,9}, stapedectomy is nowadays outdated and stapedotomy is the preferred surgical treatment for fenestral otosclerosis with good cochlear reserve.

Traditionally, modern stapes surgery through stapedotomy involves the use of a microscope and a transcanal approach under local anaesthesia. The procedure includes preparing the tympanomeatal flap, removing part of the bony frame to visualise the ossicular chain (stapes, incus, second portion of the facial nerve, pyramidal eminence), removing the stapes superstructure, preparing the footplate hole, placing the piston prosthesis between the incus and the footplate hole, and finally repositioning and packing the tympanomeatal flap.

For an optimal surgical result, it is crucial to carefully analyse every step and aspect of the procedure.

Patient position

Traditionally, the patient should be supine on the operating table with the head hyperextended and rotated to expose the ear to be operated (Fig. 1). The surgeon stands very close to the patient, resting their wrists on the patient's head to minimize hand movement errors. Even in the paper by Mantokoudis and colleagues that recently revised classical microscopic transcanal approach in stapes surgery, the positioning of the patient is considered a crucial step in the surgical procedure ¹⁰. In our opinion, furthermore, the operating table should be placed as low as possible and tilted in a reverse Trendelenburg position, with the headrest angle maximally reclined.

Instruments to visualise: microscope and endoscope

The first documented use of a binocular microscope in otologic surgery is attributed to Gunnar Holmgren in 1922. However, Emilio De Rossi is often cited as the first to use a binocular magnification system in 1869, although it consisted of a single lens rather than a true binocular microscope. Carl Olof Nylen was the first to use a monocular microscope in 1921, which was quickly replaced by Holmgren's binocular model ¹¹.

Afterwards, the evolution of the binocular operating microscope in otologic surgery marked a significant advancement, enabling a less invasive transcanal approach to the mid-

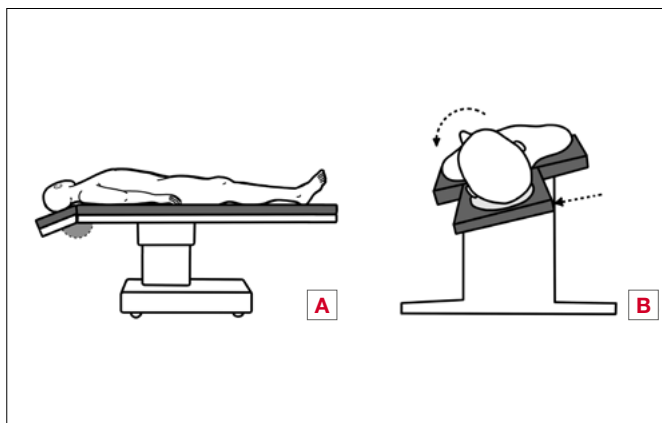


Figure 1. Patient positioning for stapes surgery: **A)** the patient should be positioned supine on the operating table with the head hyperextended and rotated to expose the ear to be operated; **B)** to obtain a better exposure, the table can be tilted on the frontal (coronal) plane.

dle ear. Previously, more invasive methods like endoaural incisions or retroauricular approaches were common. Although it limits the working space, a transcanal microscopic approach provides binocular vision into the middle ear without needing an extensive skin incision, thus reducing postoperative pain and bleeding. Moreover, this minimally invasive technique avoids complications such as scar tissue formation, hypoaesthesia of the auricle, and pinna protrusion. However, its limited field of view can necessitate additional procedures, such as endoaural incisions and drilling of the auditory canal or scutum, and frequent repositioning of the surgeon and patient ^{10,12-14} (Fig. 2).

One alternative to using a microscope is endoscopy. Endoscopic surgery for otosclerosis offers a significant advantage with its wide-angle view, reducing the need for scutum removal and enhancing exposure for teaching and training ^{14,15}. This wide-angle view allows for closer and more precise visualisation of the footplate, with no or minimal bone removal and need to manipulate the chorda tympani nerve ¹²⁻¹⁴. Despite these benefits, there is currently no objective method to quantify the improved visibility provided by the endoscope, making this advantage largely subjective and based on the individual surgeon's experience. Moreover, endoscopic surgery has its drawbacks, including reduced depth perception due to its two-dimensional view and the need to operate with one hand, which can complicate the procedure and increase the learning curve ¹³. Usually, surgeons familiar with using the microscope prefer to continue with it for these reasons. Regarding the size of the endoscopes, 4 mm nasal endoscopes were initially used, but 3 mm endoscopes have become standard in otology. Studies have not demonstrated a clear superiority of narrower endoscopes, as hearing outcomes and complication rates are similar with both sizes, despite reports of better visibility with smaller endoscopes ¹⁶.

The introduction of endoscopes did not alter the fundamental surgical techniques but provided an alternative access route, with hearing outcomes remaining comparable to those of microscopic surgery. This was confirmed by systematic reviews showing no significant difference in air-bone gap closure across frequencies ^{13,14,17,18}. No significant difference in complications such as chorda tympani nerve injury, dysgeusia, or residual perforation was found between endoscopic and microscopic procedures, although some studies suggested lower chorda tympani injury rates with endoscopes due to less scutum removal ¹⁸. Despite some studies indicating higher complication rates with endoscopic surgery, also due to thermal injury, recent reviews have not found significant differences between the two ap-

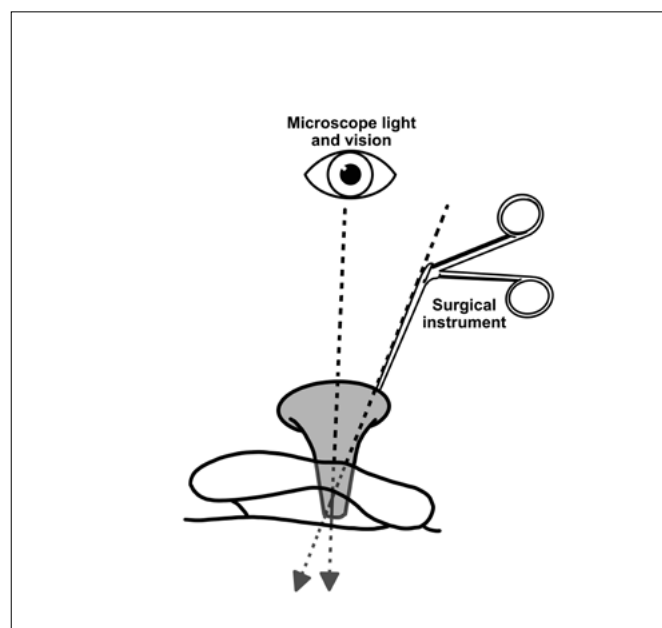


Figure 2. Microscope vision during transcanal stapes surgery.

proaches ^{13,19}. As assessed in the study by Molinari and collaborators, surgeon's experience is also a critical factor, potentially biasing outcomes, for instance leading to reduced operating times if an experienced endoscopic surgeon carries out the procedure ¹⁸.

In conclusion, while both microscopic and endoscopic approaches to stapes surgery have their pros and cons, neither can be definitively considered superior. The choice of surgical method should be based on the surgeon's expertise, training, and the availability of appropriate tools to ensure the safe execution of stapedotomy or stapedectomy.

Instruments to visualise: speculum and other approaches

In microscopic approaches, the choice of auricular speculum is crucially important. It is first useful to assess the diameter of the canal by placing an auricular speculum with a diameter of 5 mm, in order to understand whether it is reasonable to carry out a transcanal approach or if another route is indicated. In fact, a classical transcanal microscopic approach could be challenging if a narrow external auditory canal does not accept at least a 5 mm diameter speculum ²⁰. According to Mantokoudis and collaborators, the largest speculum usable according to the size of the external auditory canal and allowing visualisation of the hammer handle anteriorly and the posterior wall of the ear canal posteriorly should be preferred ¹⁰. The instruments must be held like a

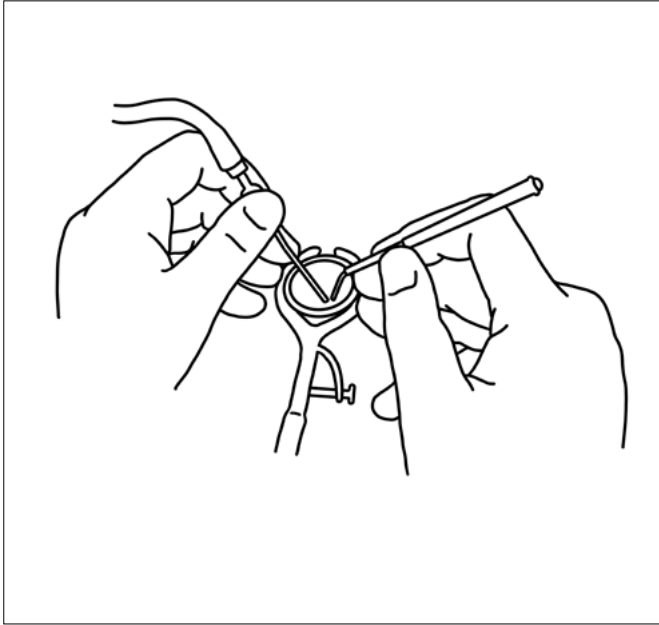


Figure 3. Hand and speculum position for transcanal stapes surgery. The instruments must be held like a pencil with the first three fingertips, stabilising the hand on the speculum or the patient's head with the other two fingers.

pencil with the first three fingertips, stabilising the hand on the speculum or the patient's head with the other two fingers¹⁰ (Fig. 3). Even if not all the surgeons use it, a speculum holder – consisting of a mobile extension mounted on the operating table – can be used to fix the speculum thus simplifying the surgeon's bimanual actions¹⁰.

An alternative way to stapes surgery is the endoaural approach, especially by an intertragal incision. This method allows surgeons to bypass the need for an auricular speculum. This type of approach can help bimanual surgery, offers a clear view of the middle ear, and can be advantageous in cases involving narrow external ear canals²¹.

Type of anaesthesia

Stapedotomy can be performed both under local and general anaesthesia. Some surgeons prefer to use local anaesthesia with or without sedation to monitor auditory and vestibular responses during surgery, while others prefer general anaesthesia for the patient's comfort.

In a 2008 study, Vital and collaborators found a higher incidence of profound HL in patients under general anaesthesia (1.8%) compared to local anaesthesia (0%)²². On the other hand, a systematic review of 417 procedures showed no significant differences in postoperative outcomes between anaesthesia methods²³.

In our opinion, local anaesthesia is preferable, since it allows the surgeon to monitor the patient's reactions during surgical manipulation of middle ear structures. Typically, 2% lidocaine with 1:100,000 epinephrine is used for its quick anaesthetic effect. About 10 mL is injected at various sites, not exceeding 7 mg/kg. Infiltration starts in the retroauricular region, blocking nerves to the outer ear, and continues between the tragus and helix, and in the posterior external auditory canal. The association with adrenaline can further reduce bleeding and improve haemostasis²⁴.

Tympanomeatal flap harvesting and scutum removal

The tympanomeatal flap should be U-shaped and created from 6 to 12 o'clock, encompassing the upper, rear, and lower walls of the ear canal^{10,25}. The skin should be incised a few mm distally from the end of the speculum. The skin of the flap is then detached up to the posterior bony annular edge^{10,25}. This step may cause bleeding, which can be controlled using an adrenaline-soaked absorbable gelatin sponge¹⁰. Accessing the tympanic cavity and detaching the tympanic membrane is best done at the posterosuperior quadrant, referred to as Rivino's engraving, where the fibrous annulus of the tympanic membrane is less adherent to the bony edge. Once the tympanic membrane has been detached from the bony rim, the tympanomeatal flap is folded anteriorly²⁵. If the surrounding bracket and structures are not sufficiently exposed, the back-top of the ear canal can be removed using a bone curette or a 2 mm low-speed diamond drill¹⁰. The structures that must be visualised before proceeding to the next step are the bracket, the long process of the incus, the tympanic part of the facial nerve, and the pyramidal eminence with the tendon of the stapedius muscle¹⁰.

Removing the superstructure of the stapes

The traditional stapedotomy procedure involves removing the superstructure of the stapes before creating an opening into the footplate and inserting the prosthesis. In 1987, Fisch proposed to reverse these steps during stapedotomy to reduce the risk of a floating footplate, inner ear damage, and dislocation of the ossicular chain⁹. Instead of removing the stapes superstructure first, Fisch proposed performing the fenestration first and then placing the prosthesis, keeping both the incudostapedial joint and stapedius tendon intact. Once the prosthesis is secured, the stapes and the lenticular process of the incus are separated, the stapes crura is fractured, the stapedius tendon is cut, and the superstructure is removed. This reversal of steps decreases the exposure time of the vestibule, minimises blood entry, and reduces the need for manipulation and the risk of inner ear injury. An

additional benefit of Fisch's reversed steps stapedotomy is the increased stability of the ossicular chain, making it easier to position the piston on the long process of the incus⁹. In 2008, Fiorino and Barbieri described a reversal steps stapedotomy technique with early removal of the posterior crus. In our opinion, this technique can provide better visualisation of the stapes footplate and, simultaneously, by retaining the anterior crus of the stapes until after the prosthesis is secured, the technique maintains the stability of the ossicular chain throughout the procedure²⁶.

Performing the footplate hole

The next surgical step is creating the footplate hole. Fenestration techniques in stapedotomy have advanced significantly with the introduction of microdrills and lasers, moving beyond conventional manual drills (Trefine)¹⁰. Historically, manual drills were widely used and favoured due to their familiarity among surgeons and their simplicity, especially when dealing with thin footplates. The advent of microdrills marked a certain improvement in stapedotomy, particularly in shortening the operation time, especially when the footplate is very thick. Microdrills, equipped with small diamond burs of 0.6-0.7 mm in diameter, operate with low noise intensity and low torque, making them a safer option for footplate drilling without causing significant acoustic trauma. This was shown in numerous recent studies²⁷⁻³¹. Studies have further demonstrated that microdrills can create precise, round holes that match the size of the prosthesis, reducing the risk of fistula and granulation tissue formation²⁹, as well as that they result in better audiological outcomes compared to manual drills³⁰. However, despite their benefits, microdrills also present certain risks, such as the possibility of advancing into the vestibule and causing sensorineural HL and vertigo²⁷. Additionally, their use in endoscopic surgery is complicated by reduced depth perception, leading to longer operation times³².

The introduction of lasers in stapedotomy in the 1980s aimed to minimise mechanical manipulation of the footplate and inner ear³³. Lasers allow for soft touch or no-touch-at-all perforation of the footplate, thereby reducing the risk of mechanical trauma^{34,35}.

Various types of lasers, including argon, diode, KTP, thulium, and CO₂, offer distinct characteristics that cater to different surgical needs. Laser technology provides high precision, a bloodless surgical field, and the ability to cut, vaporise, and coagulate tissue using thermal energy. Despite these advantages, lasers also pose potential risks, such as overheating of the perilymph, acoustic trauma, and other complications specific to each laser type. Furthermore, the

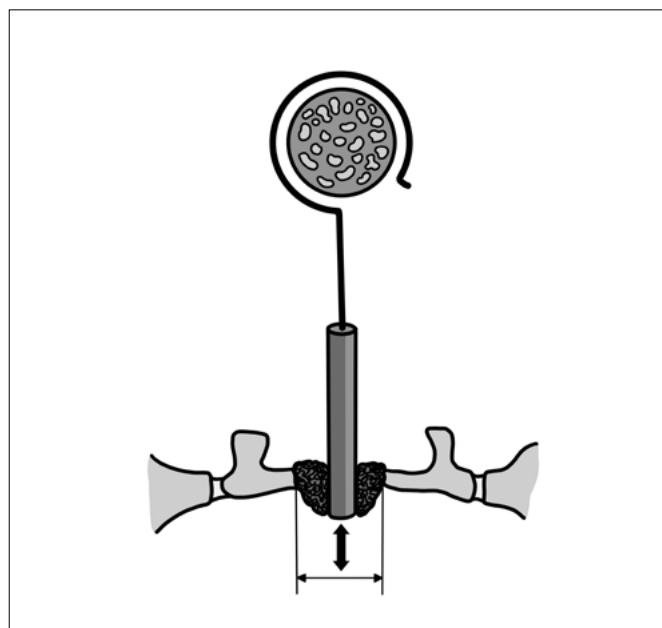


Figure 4. Vibration model of a piston stapes prosthesis.

high cost and need for specialised training and equipment can be limiting factors³⁵.

Comparative studies have yielded mixed results regarding the superiority of microdrills and other conventional methods over lasers. On the other hand, research comparing laser techniques with conventional methods showed varied outcomes. Silverstein and colleagues reported improved audiological outcomes with the KTP laser, but noted prolonged dizziness and instability in some patients³⁶. Similarly, Arnoldner and collaborators found that while hearing results were comparable, the incidence of perilymphatic fistula was higher in laser-assisted surgeries³⁷. Other studies, such as those by Pauli and colleagues and Altamami and colleagues, found no significant differences in hearing thresholds between different surgical techniques involving the use of lasers^{38,39}. A systematic review by Wegner and collaborators in 2013 reported no evidence that laser techniques were superior to others in postoperative hearing outcomes, even if the rates of footplate fracture and sensorineural hearing damage seemed to be increased with the use of perforators or microdrills⁴⁰.

Moreover, even if each type of laser used in stapedotomy has unique characteristics, there is no conclusive evidence proving the clinical superiority of one laser type over another or over traditional techniques⁴⁰. In the systematic review by Wegner and colleagues, it also emerged that many studies suffer from biases, small sample sizes, and methodolog-

ical inconsistencies, making it difficult to draw definitive conclusions⁴⁰. In the absence of robust evidence, the choice of operative technique often depends on the surgeon's preference, experience, and specific clinical circumstances.

Characteristic of the piston

The rigidity of the annular ligament constitutes 90% of the total impedance in the human middle ear at lower frequencies, thereby playing a crucial role in sound transmission, particularly for speech frequencies. The solid collagen fibres of the annular ligament significantly influence the amplitude of stapedial vibrations during low-frequency acoustic stimulation. The sound pressure at the cochlear entrance correlates directly with the volume velocity of the stapes, which is defined by the product of the area and amplitude of the vibrating footplate. With an area of approximately 3.2 mm², the footplate vibrates at amplitudes of only a few nanometers to displace a sufficient volume of liquid to transmit sound pressure into the cochlea under physiological conditions^{41,42}. Replacing an otosclerotic stapes with a piston prosthesis eliminates the annular ligament as the primary impedance factor in the middle ear, allowing the ossicles to vibrate with greater amplitudes at equivalent sound pressures at the tympanic membrane. Consequently, a piston prosthesis with a smaller contact area, such as a 0.4 mm piston, can vibrate with a much larger amplitude at equivalent sound pressures, compensating for its smaller surface area⁴¹ (Fig. 4). However, reducing the diameter of a piston is limited by the vibrational capacity of the tympanic membrane and the ossicles. Animal experiments suggest that the maximal vibrational amplitude of sound-transmitting structures is achieved with a piston diameter smaller than 0.4 mm, and volume velocity decreases with smaller diameters⁴². Clinical findings support this lower limit, with Grolman et al. reporting decreased sound transmission, especially below 1 kHz, for a 0.3 mm compared to a 0.4 mm piston⁴³. Pistons with diameters of 0.4 mm and greater generally exhibit similar sound transmission properties if the vibrational capacity of the middle ear structures remains unrestricted. However, literature on the acoustic results following stapedoplasty with various piston diameters is inconsistent. For instance, Fisch⁹ and Shabana et al.⁴⁴ found no significant difference in hearing outcomes at speech frequencies between 0.4 and 0.6 mm pistons. In contrast, as reported in Hüttenbrink review, a significant advantage for the larger diameter at 500 Hz was observed, although both diameters performed equally at higher frequencies⁴¹. Other studies, such as those by Häusler, and Coletti et al., have reported varying results, indicating better performance

at different frequencies depending on the piston diameter used^{41,45}. Mathematical models have also been used to predict the impact of piston diameter on sound transmission, generally suggesting that larger diameters may offer advantages. However, these models often rely on experimental data with inherent methodological discrepancies, leading to varying results. These studies must be carefully interpreted, as inaccuracies in parameter estimation can distort results. The vibrating area in stapedoplasty is not solely defined by the piston's diameter, as the surrounding connective tissue membrane also contributes to sound transmission (Fig. 4). Clinical audiology, in fact, typically does not register large deficits after stapedoplasty with a 0.4 mm piston, despite theoretical predictions of significant losses. Fucci et al. found that 0.4 and 0.6 mm steel pistons inserted into identically sized fenestrations performed equally well⁴⁶.

Moreover, many studies comparing acoustic outcomes with different piston diameters do not specify the size of the footplate fenestra, and most surgeons aim to perforate the footplate slightly larger than the piston diameter to minimise inner ear trauma. The area that vibrates the labyrinthine fluids is actually determined by the size of the footplate hole, not the diameter of the piston⁴⁷, and this aspect could lead to bias.

The material of the piston may also impact on the acoustic performance. Heavier prostheses, like those made from steel or gold, tend to perform better at lower frequencies, while lighter materials, such as Teflon, transmit sound more effectively at higher frequencies. This effect is due to shifts in the resonance frequency of the reconstructed middle ear^{43,48,49}. However, the overall influence of piston mass on sound transmission is relatively minor, as even significant increases in mass result in less than a 10 dB reduction in transmission. This minor influence was demonstrated in early animal experiments⁵⁰ and later supported by mathematical models⁴⁷ and temporal bone studies^{51,52}, although some of these studies reported contradictory data⁴¹. In any case, surgeons currently use only lightweight prostheses. Therefore, the only fundamental principle behind prostheses used in otosclerosis surgery is to create a secure connection between the mobile long process of the incus and the perilymph in the oval window. Since Shea and Treace first introduced a Teflon stapes replica in 1956³, many types of stapes prostheses have been developed. Advancements in surgical materials, including those with greater biocompatibility, have played a key role in the development of new prostheses. Innovations like shape-memory prostheses were also introduced⁵³, as well as non-ferromagnetic implants for magnetic resonance compatibility⁵⁴.

Fritsch and Naumann classified stapedectomy prostheses into 4 categories: wire loop, piston, bucket, and home-made⁵⁴. Commercial prostheses (wire loop, piston, and bucket) typically consist of 3 parts: the incus attachment end, the shaft, and the oval window attachment base⁵⁴. Innovations in these areas have aimed to prevent complications like incus necrosis, often caused by ischaemia from pressure during crimping or foreign body reactions, as well as dislocation, and maximise hearing outcomes as well as facilitate the surgeon's work during the procedure⁵⁴.

Materials used for stapes prostheses include stainless steel, platinum, titanium, nitinol, and Teflon. Stainless steel is chosen by some surgeons for its rigidity, shape retention, and malleability. Platinum, although malleable, has been associated with higher incus necrosis rates, possibly due to local toxicity⁵⁴. Titanium is lightweight, rigid, and biocompatible, forming a protective titanium oxide layer upon oxidation, reducing granulation and scar tissue formation. Nitinol prostheses, made in a nickel-titanium alloy, which revert to their original shape when heated, offer advantages in fixation but its nickel content may raise concerns about biocompatibility, even if some studies seem to reject this hypothesis⁵⁵. Teflon, a common material, is chemically stable, malleable, and resistant to corrosion, with a 'memory effect' that minimises incus necrosis due to ischaemia. Comparative studies have shown no significant differences in audiologic outcomes between various materials^{49,56,57}, or in the rate of complications⁵⁷.

Some prostheses come in predefined sizes, while others can be trimmed to fit during surgery. Shaft diameter can also vary. Some studies suggest better hearing results with larger diameter prostheses, although the choice often depends on the surgeon's skill and the specific case⁵⁸. As described by Fisch in 1994⁵⁹, and confirmed by the review from Hüttenbrink in 2003⁴¹, the length of the stapes prosthesis should be calibrated so that approximately 0.5 mm of the prosthesis extends into the vestibule. This length should help to prevent the prosthesis from dislocating during lateral movements of the incus, such as those caused by sneezing or during a Valsalva manoeuvre. Additionally, it safeguards the delicate structures of the inner ear, particularly the utricle and saccule, from damage when the incus moves medially, as might occur during an increase in atmospheric pressure.

Crimping of the prosthesis

One of the critical steps during stapes surgery is the coupling or crimping of the prosthesis onto the incus (Cover figure). Improper crimping, whether too tight, too loose, or causing mechanical trauma during the process, can po-

tentially lead to incus erosion^{60,61}. Furthermore, both experimental and clinical studies have demonstrated that the quality of crimping is directly associated with postoperative hearing outcomes⁶². Consequently, various prostheses have been developed with different crimping methods. Current stapes prostheses can be categorised into self-crimping and manually crimped types. Self-crimping options eliminate the need for manual crimping and its potential complications, even if the incus end loop diameter of these types of prosthesis is often predefined and in our opinion cannot always adequately fit all subjects.

Initially, some prostheses, such as bucket-handle and cup prostheses, as well as Teflon self-crimping prostheses, were designed to couple with the incus without additional crimping. More recently, shape-memory heat-crimping prostheses made from a nickel-titanium alloy known as nitinol have been introduced⁶³. These prostheses are crimped by applying heat via a laser or bipolar forceps, which activate the shape-memory properties of nitinol, causing the prosthesis loop to close. Using a laser-crimped nitinol prosthesis avoids direct contact with the prosthesis or the incus, thereby preventing trauma that may occur with manual crimping⁶⁴.

Even if manual crimping is technically more challenging, heat crimping can also have drawbacks, such as the potential for vaporisation of blood vessels, leading to necrosis of the long process of the incus⁵⁵. The effect of various crimping methods on hearing outcomes after stapes surgery has been the focus of numerous studies, although the quality of these papers is relatively low^{63,65-68}. Most of these studies are small and do not reach statistical significance. Among those that do, the findings consistently favour heat-crimped prostheses over manually crimped ones, and manual crimping over no crimping. None of the crimping methods appear to increase the incidence of adverse events⁶². Until further high-quality studies with sufficient follow-up duration are conducted to confirm these findings, it is reasonable for surgeons to use the type of prosthesis and crimping method with which they feel most comfortable⁶².

Sealing of the footplate

The necessity of sealing the oval window is debated, with some studies suggesting that a well-executed technique is more important than the use of a sealant for preventing perilymphatic fistula⁶⁹. However, some surgeons choose not to seal the oval window at all, as the additional step may complicate an otherwise straightforward procedure⁶⁹.

Different materials for sealing the oval window in stapes surgery exist, both autologous and heterologous, all with

advantages and drawbacks. The principal autologous are fat, vein, fascia, perichondrium, and blood clot. The most widely used are heterologous represented by hyaluronic acid, gelatin sponge, and the acellular porcine-derived matrix ⁶⁹.

Fat is seen as a practical and effective option for sealing, being both cost-effective and stable over time, with outcomes similar to other autologous tissues like vein and fascia. The use of vein grafts, which are compatible with middle ear mucosa and stable over the long term, is well-established. Veins are traditionally harvested from the wrist or hand, but using the superficial temporal vein offers better cosmetic results and convenience by utilising the same operative site ⁶⁹. Gelfoam, introduced by House for stapes surgery ⁷⁰, is easy to handle and widely available. It does not require an additional surgical incision, thus reducing surgical time and associated risks. However, it can cause adhesions and fibrosis, especially in inflamed or exposed mucosa. Some studies have shown no significant difference between using Gelfoam and not sealing at all, leading some practitioners to stop using it. Autologous materials such as perichondrium and fascia are also cost-effective and compatible with the middle ear, although harvesting these tissues can extend the duration of surgery ⁶⁹. There are concerns about the chondrogenic potential of perichondrium, but these can be mitigated with proper handling. Scarpa et al. found that hearing outcomes and vestibular complication rates are similar regardless of the sealant used, suggesting that the choice of material should be based on the surgeon's preference, as no clear evidence favours one material over another ⁶⁹. The authors of the present review drop only a blood clot to seal the footplate.

Special conditions

Age – Stapes surgery is a safe and effective treatment for any age, once stapes fixation is confirmed. There is not a superior ⁷¹ or inferior ⁷² age limit for undergoing such a procedure.

Chefs and sommeliers – Stapes surgery should be carefully counselled in chefs and sommeliers due to the risk of permanent taste disorders. Alternative treatments like hearing aids should be considered. If surgery is chosen, patients must be informed of the potential loss of work function ⁷³.

Aviation – Thiringer and Arriaga studied 16 US Air Force aircrew members who returned to flight duty post-stapedectomy without complications ⁷⁴. Katzav et al. reported similar success in Israeli Air Force pilots ⁷⁵. While military pilots in Brazil are deemed unfit post-surgery, civil aviation does not restrict stapedectomy, although those with permanent vestibular disorders cannot be certified ⁷⁶.

Diving – Scuba diving may increase the risk of perilymphatic fistula and prosthesis displacement. Studies show no significant risk, but 54.3% of surgeons recommend permanent diving restrictions after stapes surgery. Despite some postoperative otologic symptoms, no strong evidence links these to diving ^{76,77}.

Conclusions

This narrative review on stapes surgery provides an overview of this surgical procedure, highlighting both historical and modern advancements. Below are some personal considerations based on the comprehensive content presented. The historical evolution of stapes surgery is a testament to the relentless pursuit of medical innovation. Starting from Valsalva's initial identification of stapes fixation to Shea's introduction of the Teflon prosthesis, each advancement has been built on the shoulders of previous discoveries. The shift from microscopic to endoscopic techniques represents an appreciable technological step. Endoscopy offers certain advantages, but also has some limitations, such as reduced depth perception and the need for one-handed operation.

The choice of technique for creating the footplate hole, whether using manual perforators, microdrills or lasers, remains a topic of debate. While microdrills offer precision and reduced operation times, they carry risks such as vestibular penetration. On the other hand, lasers minimise mechanical trauma but present challenges like potential overheating and higher costs. The variety of prosthetic designs, dimensions and materials reflects the complexity and individuality of medical practice. The fact that no single type or material has emerged as superior underscores the importance of a personalised approach. Surgeons must weigh the benefits and drawbacks of each type of prosthesis based on the specific patient characteristics, as well as their own surgical experience. The advancements in design of the prosthesis, particularly the move towards lighter and more biocompatible materials, and the possibility of self-crimping technologies, have not only enhanced the functionality of this surgical procedure, but also reduced the risk of complications. The ongoing evolution of stapes surgery is a reminder that medical practice is never static, and that continuous improvement is vital for achieving the best possible patient outcomes. It is also important to underline the importance of historical knowledge, technological innovation, and ongoing research in the field, which is essential for practitioners to provide the highest standard of care in otologic surgery.

Conflict of interest statement

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Author contributions

LB, FL, ADV: conceived the initial idea for the narrative review and developed the structure of the article; FF, SB: performed the literature review and critically analyzed the sources. All authors contributed significantly to drafting the manuscript, revising it for important intellectual content, and approving the final version to be submitted. Each author has read and agreed to the published version of the manuscript.

Ethical consideration

Not applicable.

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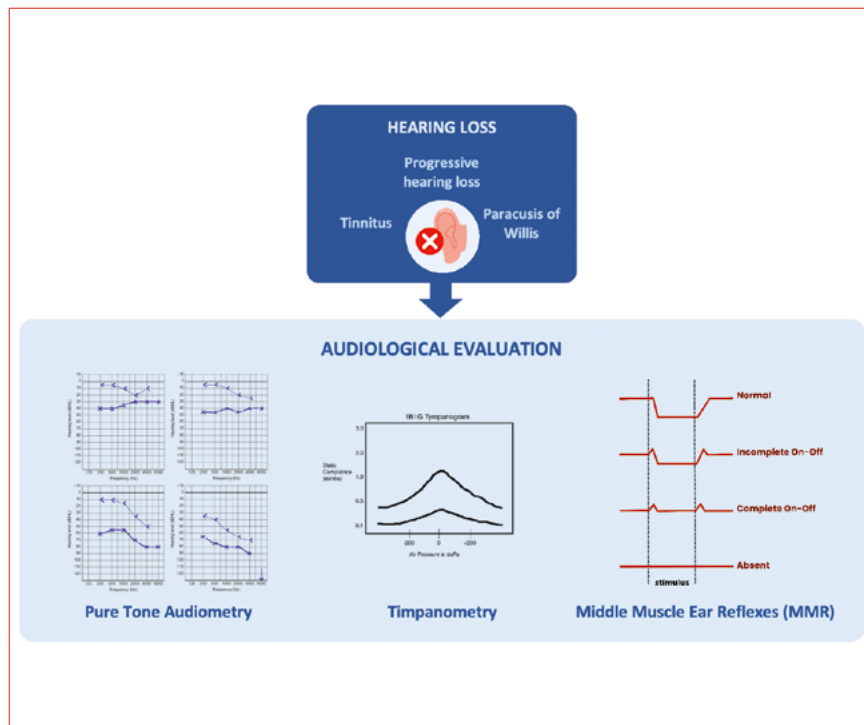
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Issues in the audiological assessment of otosclerosis

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Cover figure. The image summarises the essential tools used to diagnose and characterize hearing impairment in otosclerosis.

Summary

Otosclerosis is a temporal bone disease characterised by abnormal bone remodelling of the otic capsule. Typically, it presents as progressive conductive hearing loss, while sensorineural hearing loss may develop as the disease progresses. Diagnosis is challenging as no single diagnostic tool provides high specificity and sensitivity for otosclerosis. Instead, a battery of tests is used as proper diagnostic workup: pure-tone audiometry, tympanometry, and acoustic reflex tests are fundamental, while imaging, particularly high-resolution temporal bone computed tomography, enhances diagnostic specificity. Differential diagnosis should exclude middle ear pathologies, ossicular chain anomalies, osseous dystrophies, and inner ear disease such as third window disorders. As a result, a comprehensive, integrated diagnostic approach combining audiological and imaging techniques is essential for accurate diagnosis and effective planning of treatment in otosclerosis.

Key words: otic capsule, conductive hearing loss, middle ear muscle reflex, paracusis of Willis, tinnitus

Introduction

The term otosclerosis was coined by Politzer to describe a primary disease of the labyrinthine capsule, which was originally believed to be a condition attributed to “chronic interstitial middle ear catarrh” with secondary stapes fixation¹. Despite his publication of histologic evidence of otosclerosis in 16 cases of stapes fixation, it took almost half a century for Politzer’s views to gain universal acceptance². Otosclerosis, a process of progressive pathologic bone remodelling affecting only the temporal bone, is one of the most complex diseases that leads to hearing loss (HL). It is characterised by abnormal remodelling in the otic capsule, particularly the fissula ante fenestram, but may extend to the region of the labyrinth and cochlea, oval, and round window^{3,4}.

The classic presentation of otosclerosis consists of progressive conductive HL (CHL) in adulthood, which is worse at low frequencies especially early in the disease. This is explained by the effect of the impaired vibrancy of the footplate in the lower frequencies. It occurs bilaterally in 80% of patients, although unilateral involvement is often present early in the disease.

The progression of otosclerosis should be monitored by an audiogram because it directly correlates to HL. As the stapes footplate becomes fixed to the oval window, the CHL worsens, and the air bone gap (ABG) increases and begins to involve all frequencies.

However, the type of deafness depends on the location and extension of the otosclerotic foci: lesions that originate in the fissula ante fenestram and involve the annular ligament cause conductive deafness, whereas medial progression to the cochlear endosteum causes sensorineural deafness. Therefore, when the course of otosclerosis deviates from the classic presentation, especially in the retrofenestral subtypes of the disease, mixed HL (MHL) or only sensorineural HL (SNHL) might occur^{5,6}.

Tinnitus is a highly prevalent symptom, and patients may describe improved hearing clarity in noisy environments. This phenomenon is known as paracusis of Willis, in which the CHL subdues the background noise such that it improves the signal-to-noise ratio for the patient.

Vestibular symptoms have been reported in up to 40% of patients with otosclerosis. They should be accurately investigated during clinical evaluation, since they can conceal pathologies mimicking otosclerosis, such as Ménière’s disease, an enlarged vestibular aqueduct (EVA), or superior semicircular canal dehiscence (SSCCD)⁴.

A correct assessment of the disease is of utmost importance as it has the potential to lead to earlier diagnosis, referral,

and treatment. Precise and accurate audiologic evaluation is fundamental to a proper surgical approach: otologists rely on the precision of the audiologic results and determination of the degree of the conductive component. Therefore, a precise audiologic work-up is a crucial part of the diagnostic protocol for otosclerosis (Cover figure).

Audiological diagnosis of otosclerosis

It must be clarified that there are currently no preoperative diagnostic evaluations specifically tailored for otosclerosis that can achieve sufficiently high levels of specificity or sensitivity for the disease. Nonetheless, combining multiple examinations, as a test battery, may aid in differential diagnosis and can generate a considerable clinical suspicion for otosclerosis.

Since the advent of modern stapedectomy pioneered by Shea in the 1950s, there have been significant advancements in diagnostic testing and a deeper comprehension of how concurrent otologic conditions can influence surgical outcomes. Audiological characteristics play a crucial role in diagnosing clinical otosclerosis. Generally, pure-tone audiometry, tympanometry, and acoustic reflex tests serve as diagnostic tools. The clinical diagnosis of stapes fixation hinges on various factors such as case history (progressive HL, tinnitus, paracusis, familial history, etc.), normal otoscopic findings, CHL and/or MHL, type A or As tympanograms, and the absence of the middle ear muscle reflex (MMR).

However, the combination of normal otoscopy with CHL is not exclusive to otosclerosis, with similar presentations being observed in cases of middle and inner ear anomalies. Further, a CHL with normal tympanogram and absent MMRs may be present in some middle ear or ossicular chain diseases. As a consequence, comprehensive audiological preoperative assessment is crucial for a correct approach.

Pure tone audiometry

In otosclerosis, stapes fixation and resultant stiffening of the ossicular chain almost always produces HL, particularly for lower frequency sounds. Typical findings from pure tone audiometry reveal a CHL, where air conduction sensitivity is notably poorer compared to bone conduction. A typical audiological sign of otosclerosis is the “Carhart notch”, a lowering of the bone hearing level up to 25 dB at 2 kHz; it has historically been considered an indicator of otosclerosis, but it is not pathognomonic of the disease⁷. This artificial sensorineural component is caused by the missing resonance of the middle ear whose maximum is located by

2 kHz. Therefore the “Carhart notch” disappears postoperatively⁸. Recent investigations have raised 3 general inquiries regarding the diagnostic significance and specificity of notching deficits in bone conduction thresholds at 2000 Hz. Firstly, reductions in bone conduction thresholds are often observed at other frequencies in otosclerosis patients. Additionally, the presence of a Carhart notch at 2000 Hz is not consistently observed in all cases of otosclerosis or ossicular chain fixation. Lastly, concerning this second point, patients with causes of CHL distinct from otosclerosis may exhibit a notch in bone conduction thresholds at 2000 Hz⁹. In advanced stages of otosclerosis, CHL progresses to MHL. Furthermore, in cases with cochlear involvement, moderate to profound SNHLs are encountered.

To determine the presence of ABG and its entity holds significant importance, mainly for surgical indications. Particularly notable is its gradual decline towards higher frequencies, which is indicative of the elastic rigidity of the ossicular chain, a crucial factor in stapes ankylosis.

The tuning fork tests may be useful to confirm the presence of an ABG. They are based on the same physical principles as the audiometric measurements and are very simple and quick to execute. Among tuning fork tests, Weber’s and Rinne’s tests are the most widely used. Weber’s test lateralises to the affected ear, whereas Rinne’s test is negative in the affected ear in the case of a CHL^{9,10}.

Another procedure to be mentioned is the sensorineural acuity level (SAL) test. The SAL test provides valuable clinical information for better definition of cochlear reserve and the entity of the ABG, particularly in cases in which it is difficult to precisely evaluate the bone conduction threshold. The SAL test plays a unique role in clinical audiology when performed with insert earphones and used as a supplement to conventional bone-conduction measurements to confirm ear-specific information on sensory hearing thresholds⁹.

Impedance audiometry: tympanometry and middle ear muscle reflexes

Immittance measurement has been a longstanding tool in evaluating middle ear disorders. It comprises tympanometry and MMRs assessment. In individuals with otosclerosis, a common presentation includes type As (shallow type A tympanogram) or normal type A tympanograms, and absent MMRs.

At present, tympanometry is primarily conducted using a conventional low probe tone frequency. However, tympanometry carried out at this conventional low probe tone frequency (226 Hz) often fails to detect lesions that specifically impact the ossicular chain. For instance, the tympanogram yielded by a conventional 226 Hz tympanogram is

typically insufficient to distinguish between a normal middle ear and ears affected by otosclerosis (stapes fixation). It has been shown that an abnormality is most clearly seen when the probe tone frequency approaches the resonant frequency. Middle ear pathologies, such as otosclerosis, affect the resonant frequency of the middle ear system, and in patients with otosclerosis it has been demonstrated a shift to higher frequencies of the resonant frequency of the middle ear. Therefore, using a probe tone near the resonant frequency may provide the most useful information regarding the differential diagnosis of middle ear pathologies. Several clinical and laboratory studies have reported prominent differences between healthy and otosclerotic ears when using higher probe tone frequencies⁹.

In this regard, the introduction of multifrequency tympanometry (MFT) has facilitated tympanometry across a broad spectrum of probe tone frequencies. Recent research indicates that the identification of otosclerosis (or stapes fixation) is enhanced by employing measures derived from multifrequency tympanometry or by combining tympanometric variables in specific configurations^{9,8}.

Furthermore, several studies have indicated narrower tympanometry peaks, at traditional low tone probe frequency in ears affected by otosclerosis compared to healthy ears.

MMR assessment serves as a valuable adjunct to tympanometry for detecting the presence or absence of middle ear disorders, including otosclerosis. First described in humans by Lüscher in 1929, with practical testing outlined by Metz in 1946, MMR testing involves monitoring stapedius muscle contraction elicited by high-intensity auditory stimuli. The absence of MMR in the probe ear is attributed to the inability to monitor changes in immittance due to stiffening of the ossicular chain, preventing measurable changes in immittance resulting from stapedial muscle contraction. In otosclerosis, the affected ear will lack reflexes with both ipsilateral and contralateral stimulations. Conversely, MMRs in the affected ear indicate a mobile stapes footplate and ossicular chain, allowing practitioners to screen for other potential causes of CHL. In cases of unilateral otosclerosis, MMR is typically absent when the stimulus and probe tone are presented to the affected side (ipsilateral mode). However, MMR may be elevated or absent in the contralateral mode, depending on the severity of the CHL. Finally, the contralateral MMR in the unaffected side is also absent when the probe is placed in the affected side^{8,9}.

In the early stages of otosclerosis, a biphasic reflex response (an on-off effect) has been observed, even before the onset of an ABG. This biphasic MMR response is characterised by a sudden increase in admittance upon switch-

ing the stimulus on and off, surrounding a central plateau at 0¹¹. An “incomplete” or “partial” on-off effect is characterised by the appearance of a more or less extensive negative deflection between the 2 positive deflections, simulating a normal reflex. This type of response is a transitional form between normal reflex and “complete” on-off effect and is closely related to the evolution of the oval window stapedial otosclerotic focus¹¹.

Finally, it must be mentioned that MMR can be normally present in otosclerosis if no focus affects the oval window¹¹.

Wideband acoustic immittance (WAI)

WAI represents a novel method for assessing the middle ear that allows researchers and clinicians to quantify the energy reflected or absorbed in the ear canal across a broad frequency range, typically spanning from 250 to 8000 Hz. Power absorbance (PA) is a ratio of absorbed power over the incident power and varies between 0 and 1. A value of 0 means all sound energy has been reflected and a value of 1 means all sound energy has been absorbed by the middle ear system. WAI offers several potential advantages over conventional tympanometry; notably, it measures across a wide frequency range (250-8000 Hz) and boasts rapid and easy testing, typically requiring only a few seconds to complete.

In comparison to conventional 226 Hz tympanometry, WAI exhibits significantly greater sensitivity to ossicular pathologies. Additionally, the patterns of absorbance vary depending on the condition of the middle ear, resulting in distinct absorbance patterns for different pathologies. Typically, a stiffening pathology leads to reduced absorbance over a specific frequency range. For instance, otosclerotic ears often display markedly increased reflectance between 400 and 1000 Hz. Shahnaz et al.¹² have determined that PA represents the most effective method for identifying ears with otosclerosis compared to 226 Hz and multifrequency tympanometry. In their study, PA successfully identified otosclerosis in 82% of the sample with a false positive rate of 17.2%¹². The research indicates that incorporating PA alongside other tools for assessing middle ear function will enhance the identification of otosclerotic ears in clinical practice^{9,12}.

Other diagnostic tests

Regarding speech perception, word recognition scores in quiet are good or excellent in most patients with otosclerosis, even in those with some apparent deficit in bone conduction hearing thresholds. While speech audiometry can offer valuable insights into speech comprehension, it is not obligatory for the preoperative assessment of otosclerosis. However, its execution is advisable in cases exhibiting a

bone conduction threshold shift (MHL, SNHL) to either exclude or confirm the presence of the roll-over recruitment phenomenon. In selected cases it may be also helpful in the choice of the ear to be operated. Conversely, if hearing devices selection and fitting become necessary, speech audiometry becomes imperative⁸.

Transient-evoked otoacoustic emission (TEOAE) or distortion product otoacoustic emission (DPOAE) measurements offer no relevant diagnostic assistance. Otoacoustic emissions (OAEs) cannot be recorded in individuals with middle ear dysfunction, including those with ossicular chain fixation and otosclerosis. Nevertheless, several recent publications have discussed a potential application for OAEs in assessing auditory function after “microtraumatic stapedotomy”. Despite variations in findings across studies and between patients, some reports suggest the appearance of detectable OAEs in the frequency range of 1000 to 1500 Hz, possibly linked to the normalisation of the middle ear’s resonance frequency following microtraumatic stapedotomy⁸.

Study of vestibular evoked myogenic potentials (VEMPs) is useful in distinguishing otosclerosis from some inner ear pathologies that can cause a conductive gap, the most frequent being EVA and SSCCD, where VEMPs responses are present, generally with lower thresholds and higher amplitudes¹³. The evaluation of VEMPs thresholds can be added in the diagnostic work-up of suspected otosclerosis in case of doubt, narrowing down the differential diagnosis in patients with “pseudo-conductive” components, and reducing costs by preventing unnecessary radiation exposure and unsuitable middle ear surgery¹⁴. Even if this approach may avoid unnecessary middle ear surgery for ABGs with unknown causes, the exact diagnostic role of VEMPs testing in this field requires further systemic examinations^{9,13,14}. Regarding the elicitation of VEMPs in patients with otosclerosis, it is generally reported that stapes fixations are associated with the absence of VEMPs. Anyway, the presence of VEMPs does not exclude otosclerosis, since despite the conductive deficit, VEMPs can be elicited in a small number of ears with otosclerosis. The air conduction-VEMPs are more vulnerable to CHL, whereas bone conduction-VEMPs are not; however, the low rate of bone conduction-VEMPs could be caused by inner ear damage¹⁴.

Discussion

Otosclerosis, an osteodystrophy of the otic capsule, can pose a diagnostic challenge, and the most exact identification of otosclerosis is still based on postoperative histopathologic analysis of the removed ankylotic stapes foot-

Table I. Differential diagnosis of otosclerosis

Middle ear pathologies	Serous otitis media
	Adhesive otitis media and tympanosclerosis
	Chronic otitis media and cholesteatoma
	Middle ear tumours
Ossicular chain anomalies	Congenital and acquired ossicular chain anomalies
Inner ear anomalies (third window disorders)	Superior semicircular canal dehiscence
	Posterior semicircular canal dehiscence
	Perilabyrinthine fistula
	Enlarged vestibular aqueduct
	X-linked stapes gusher
Osseous dystrophies	Paget's disease
	Osteogenesis imperfecta
Others	Cochlear cleft
	Juvenile otosclerosis
	Cochlear otosclerosis

plates. Classically, diagnosis of otosclerosis has been based on medical history, physical examination, and audiologic testing; furthermore, in the last decades, the role of imaging has increased, leading to higher specificity in diagnosis of the disease. As of now, there is no definitive preoperative diagnostic protocol, nor has a consensus-based approach been established; this poses a critical question from a clinical perspective, due to numerous potential differential diagnoses. Conducting precise preoperative examinations becomes paramount to avoid resorting to “blind surgery,” such as explorative tympanotomy.

Around one-third of stapes fixation cases may not originate from otosclerosis, but from congenital or acquired ossicular chain anomalies. Furthermore, it is essential to differentiate other middle or inner ear disorders from stapes fixations to prevent unnecessary surgeries or potential complications during the procedure. Finally, otosclerosis must be distinguished from other osseous dystrophies, such as Paget's disease and osteogenesis imperfecta. In Table I the main clinical pictures that must be differentiated from otosclerosis are reported.

Middle ear disorders, causing a CHL and from which otosclerosis should be differentiated, include serous otitis media, adhesive otitis media, tympanosclerosis, chronic otitis media, cholesteatoma, and middle ear tumours. These disorders are generally ruled out after accurate otomicroscopic examination and tympanometry⁸.

Serous otitis media may complicate otosclerosis. The combination of serous otitis media and otosclerosis presents difficulties in differential diagnosis, which are usually resolved only after the healing of secretory otitis media.

In tympanosclerosis, the tympanogram is generally type B (flat tympanogram), due to increased stiffness of the tympanic membrane and/or ossicular chain, but it may also be biphasic, due to the coexistence of fibrous and/or calcific thickening areas and atrophy of the tympanic membrane. In tympanosclerosis limited to the ossicles and/or oval window and/or tympanic membrane, tympanometric curves of type Ad (abnormal increase in peak gradient) may be detected, due to partial or total atrophy of the tympanic membrane and interruption of the ossicular chain from erosion of the long process of the incus, or may also be type C or As, with normal otomicroscopy. In this latter case, the differential diagnosis with otosclerosis is intraoperative.

Congenital cholesteatoma, in its initial form with an intact tympanic membrane, can mimic the audiometry and tympanometry of otosclerosis. Otomicroscopy may indicate the presence of cholesteatoma in the middle ear cavity, appearing as a translucent pearl close to the malleus. Differential diagnosis can only be made with a high-resolution temporal bone computed tomography (CT) scan. In some cases, congenital cholesteatoma can be an intraoperative finding.

Benign tumours of the middle ear such as facial nerve schwannomas in its second portion, ceruminous adenomas, tegmen tympani meningiomas, and glomus tumours in the initial phase of growth can mimic the clinical and audiologic presentation of otosclerosis. Differential diagnosis is performed using high-resolution CT, complemented in some cases (facial nerve schwannoma) with contrast-enhanced magnetic resonance imaging.

Ossicular chain congenital or acquired anomalies, may also mimic otosclerosis. The commonest congenital ossicular abnormalities include stapes fixation, followed by incudo-stapedial joint discontinuity. Other congenital ossicular abnormalities described in the literature include absence of stapes, stapes suprastructure, stapedius tendon, incus, and oval window, as well as stapes fixation to the promontory and Fallopian canal, or other various malformations. Differences in the ABG at low and high frequencies in pure-tone audiometry, impedance audiometry, and MMRs are useful for distinguishing otosclerosis from ossicular chain anomalies¹⁵. In ossicular chain anomalies, the ABG is generally larger than in otosclerosis and affects both low and high frequencies. Regarding the Carhart notch, Kan et al.¹⁵ recently reported that this may be present both in otosclerotic patients and in patients with incudo-stapedial disjunction, without a significant difference between groups. Similarly Kashio et al.¹⁶ reported that the incidence and depth of the Carhart notch were not statistically different between their stapes fixation, incudo-stapedial joint detachment, and malleus or incus fixation groups. Wegner et al.⁷ in a systematic review concluded that the Carhart notch was a useful hint for the presence of otosclerosis, but that it could not be used to confirm diagnosis. The study of MMRs is useful in differentiating otosclerosis from ossicular chain anomalies. With ossicular etiologies of CHL, acoustic reflexes change as the disease progresses. In otosclerosis, the reflexes may be initially normal, but as stapes fixation progresses, reflex amplitudes will decrease, and thresholds will increase, until eventually the reflexes cannot be longer detected. Also, in ossicular chain anomalies the MMRs may be variably present. The assessment of the on-off effect may further improve the value of MMRs in differentiating among etiologies of CHL¹⁷. However, combinations of several examinations including CT are needed for the differential diagnosis of ossicular chain diseases: subtle findings on high resolution CT of the temporal bone, such as the absence of the stapedius tendon and pyramidal process, or the small size of the oval window, may alert the clinician to these rare malformations⁷.

The aplasia of the annular ligament as a minor middle ear malformation comes along with the fixation of a stapes footplate. This diagnosis should be considered in young patients with clinical symptoms of otosclerosis. In these cases, stapedoplasty is also the preferred therapy¹¹.

In the case of traumatic interruption of the ossicular chain there may be a dislocation and detachment of the incus from the malleus or the fracture of the crura of the stapes. The audiologic differential diagnosis with otosclerosis is based solely on tympanometry indicating a type Ad tympanogram

(abnormal compliance of the ossicular-tympanic system). In incus dislocation, the stapedial reflex is absent because the interruption of the ossicular chain is located upstream of the insertion site of the stapedius muscle. If the interruption is downstream, as in the traumatic fracture of the crura of the stapes, the stapedial reflex is normally present.

The majority of patients with significant CHL, with otherwise normal otoscopic examination results, will have an ossicular aetiology of HL. However, there have been reports of patients undergoing middle ear exploration with the intraoperative finding of a normal ossicular chain, despite a significant CHL. For many years, these patients were considered as having an “inner ear CHL”. More recently, it has been found that third window disorders, such as SSCCD and EVA, can also cause CHL, and many patients with previously unclear causes of CHL have been found to have such a third window disorder¹⁸. Third window lesions classically present with auditory (HL) and vestibular (Tullio and Hennebert syndromes) symptoms and can be suspected if an ABG is accompanied by normal tympanometry and present MMRs, or if an ABG is accompanied by absent MMRs associated with other findings not typical of otosclerosis (e.g. vertigo or autophony)¹⁷. The diagnosis of third window defects is radiological: on temporal bone CT, specific anatomic defects include SSCCD, posterior semicircular canal dehiscence, perilyabyrinthine fistula, EVA, X-linked stapes gusher, and bone dyscrasias¹⁷⁻¹⁹.

Patients with SSCCD typically present with vertigo and nystagmus induced by loud noises (Tullio phenomenon) or increases in external auditory canal pressure (Hennebert sign)¹⁹. At audiometry, a characteristic ABG results from increased bone and decreased air conduction^{17,18,20}. This phenomenon occurs most significantly at lower sound frequencies (below 1 kHz), a range at which acoustic energy is readily dissipated. At higher frequencies, there is a small or no gap because proportionally less acoustic energy is shunted by the third window. VEMPs testing may show abnormally low response thresholds on the side of pathology. The effective impedance is reduced; this reduction results in increased transmission of acoustic energy to the saccule²⁰. A very rare condition is posterior semicircular canal dehiscence; this can occur sporadically or in association with superior canal dehiscence. Clinically, patients may also demonstrate the Tullio and Hennebert signs, while audiometry reveals an ABG at frequencies below 1 kHz²⁰.

Perilyabyrinthine fistula may be caused by destructive middle ear processes that erode the attenuated otic capsule, producing communication with the inner ear. When this involves the semicircular canals, vestibule, and/or scala vesti-

buli side of the cochlea, third window mechanics can result. The most common aetiology is chronic middle ear inflammation, such as cholesteatoma or otitis media, and the lateral semicircular canal is most frequently involved, due to its location directly adjacent to the middle ear. On audiometry, cholesteatoma demonstrates a characteristic ABG of middle ear origin, which is present at both low and high sound frequencies due to superimposed ossicular chain pathology. Rarely, cochlear-carotid dehiscence with the absence of the intervening bony partition can also occur. On audiometry, this condition demonstrates an ABG that is greater at lower frequencies, similar to other third window lesions. Other potential causes of perilabyrinthine fistula include trauma, surgery, and benign and neoplastic masses ²⁰.

Among third window defects, much attention has to be paid to EVA, as it represents the most frequent inner ear malformation. It can present in adulthood as a mixed HL mimicking otosclerosis, from which it can be difficult to distinguish without temporal bone CT scan. At audiometry, patients present with a complex and variable pattern of HL. The sensorineural component of HL is thought to result from potential associated cochleovestibular malformations and manifests at higher sound frequencies. The CHL results from acoustic energy dissipation through an enlarged third window where the vestibular aqueduct joins the vestibule ¹⁸. This is shown by an audiometric ABG at low frequencies but may be missed if bone conduction is not measured, particularly in young children who do not tolerate a full audiologic examination ²⁰. Wieczorek et al. ²¹ in a retrospective study underlined that an unusual history of HL, particularly when dating to childhood or MHL in patient populations less prone to otosclerosis, can raise the index of suspicion for adult EVA.

Interestingly, in 2016 Hong et al. ¹⁷ reported about the possibility of a concomitant otosclerosis and third window defect in patients with significant CHL. In their paper, the authors reported on 5 ears with concurrent radiological evidence of otosclerosis and SSCCD ¹⁷. When one considers middle ear exploration for concurrent otosclerosis and third window disorders, two issues have to be considered: if hearing can be improved significantly with middle ear surgery, given the concurrent presence of a third window disorder, and whether there is an increased risk of SNHL following stapedectomy, because of a concurrent third window disorder. The literature is sparse on this topic. Therefore, it seems reasonable to offer middle ear exploration to patients with concurrent otosclerosis and third window disorders, as long as they are counselled that there may not be complete closure of the ABG after surgery, and that especially in cases with EVA and X-linked third window a sensorineural further deficit may occur ¹⁷.

An extremely rare entity that may be a confounding factor in the diagnosis of otosclerosis is the presence of a “cochlear cleft” ²². It may mimic an otosclerotic focus on CT, and should be considered in the differential diagnosis when audiometric findings do not agree or when other radiological manifestations potentially indicate a CHL of inner ear origin. The “cochlear cleft” has been described radiographically as a curvilinear area of pericochlear hypodensity just anterior to the oval window on CT. It has been hypothesised to be related to the fissula ante fenestram, cartilaginous masses, incomplete ossification, a cleft between endosteal and periosteal bone, or related to the first ossification centre. Further studies have assessed the prevalence of the cochlear cleft in children and have shown no correlation with otologic symptoms. It is found less often with advancing age ^{22,23}. The importance of distinguishing these lesions from an otosclerotic focus lies in the fact that they preclude stapedotomy. No improvement in hearing would occur, and surgery is thus unnecessary.

Regarding osteodystrophies of the otic capsule, Paget's disease and osteogenesis imperfecta may present a clinical picture mimicking otosclerosis. Patients with osteogenesis imperfecta sometimes first present with a progressive CHL caused by bone reconstruction and consecutive fixation of the footplate. The therapy is stapedoplasty in accordance with the otosclerosis ⁸. Osteogenesis imperfecta is a congenital hereditary disorder characterised by abnormalities in collagen tissue. This condition can cause a stapedio-oval joint ankylosis that closely resembles otosclerosis. HL in osteogenesis imperfecta typically occurs in the second to third decade of life and can be conductive, mixed, or sensorineural. SNHL results from microfractures, haemorrhages, and the presence of vascular and fibrous repair tissue within and around the cochlea. Surgical intervention for stapedio-oval joint ankylosis in osteogenesis imperfecta is indicated, although the results are generally modest. Surgical management of HL in osteogenesis imperfecta poses technical challenges because the stapes footplate is fragile and covered by a thick, highly vascularised mucoperiosteum.

Cochlear otosclerosis

A rare and controversial entity that deserves mention is cochlear otosclerosis. It is defined as a focus of otosclerosis located in the otic capsule involving the cochlear endosteum and causing SNHL without any stapes fixation or any conductive component. However, Schucknecht et al. ^{24,25}, clearly showed that, when otosclerosis is sufficiently severe to involve the cochlear endosteum, it usually fixes the sta-

pes as well. If the definition of cochlear otosclerosis is accepted as the involvement of cochlear endosteum without associated stapes fixation, then the incidence among ears with pure progressive SNHL is very rare, reportedly 0.3–1%^{24,26}.

In the clinical diagnosis of cochlear otosclerosis, some criteria are suggested in the literature, such as SNHL with good speech discrimination, a family history of otosclerosis in a patient with symmetrical SNHL, and a positive Schwartz's sign²⁷. SNHL in cochlear otosclerosis may be suddenly aggravated at puberty or at periods of endocrine activity such as pregnancy, menopause, or treatment with oestrogens²⁶.

The diagnosis of cochlear otosclerosis mainly depends on temporal bone high-resolution CT^{24,26}. The fact that there are some clinical studies with imaging techniques which report patients with a pure cochlear sensorineural type of otosclerosis, while otopathologic studies indicate that this type of ear pathology is very rare, points to the need for more clinical control studies in large series.

Juvenile otosclerosis

Even if considered an adult disease, otosclerosis can appear during childhood as well²⁸. It is estimated that approximately 15% of patients with otosclerosis experienced HL before the age of 18 years²⁸. A histologic study reported an incidence of less than 1% in children aged under 5 years and 4% in children aged between 5 and 18 years²⁸, indicating that clinical expression of the disease is even lower. The main revealing feature of juvenile otosclerosis (JO) is CHL, and therefore the precision in establishing ABG, based on masking techniques and immittance evaluations, have a key role in the diagnosis. Pure tone audiometry, tympanometry, and acoustic reflexes must be combined into a test battery²⁸, especially in children as the typical CHL feature (a distinct notch-like decrease in bone conduction thresholds around 2000 Hz) is not always identified²⁸. CT is a necessary step for diagnosis and, in recent years, high-resolution cone beam CT has been used to assess middle and inner ear with a significantly lower effective radiation dose than traditional CT^{28,29}.

The rare cases of JO must be differentiated from other diseases causing CHL in children to plan proper treatment. Serous otitis media is the most frequent cause of CHL in childhood, and may be a confounding factor when coexisting with JO. To this regard, in 2016 Markou et al.²⁹ reported on a case with coexisting otosclerosis and serous otitis media, presenting with persistent CHL after resolution of the otitis.

Besides JO, other causes of stapes footplate ankylosis are congenital stapes footplate fixation (CSFF), Paget's disease, and osteogenesis imperfecta. CSFF is often non-progressive, with no clear family history, and is generally recognised at a younger age compared to JO³⁰. It can be seen as an isolated anomaly or together with other ossicular chain abnormalities³⁰. It has been associated with a greater ABG compared to JO and with poorer postoperative hearing outcomes³⁰. It is often difficult to preoperatively distinguish between the two disease entities given the similarities in presentation³⁰.

Conclusions

A diagnosis of otosclerosis can usually be easily established through a comprehensive clinical approach, combining medical history, pure tone audiometry, impedance audiometry, and assessment of MMRs. However, it can sometimes pose diagnostic challenges, so that an integrated diagnostic approach is essential, especially for dealing with ambiguous cases. This approach not only requires extensive audiologic examination, but also, in selected cases, the use of imaging techniques, particularly high-resolution CT, for accurate differential diagnosis and to plan appropriate treatment.

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

FF, SC, ADV: conceived the initial idea for the narrative review and developed the structure of the article; LB, FL: performed the literature review and critically analyzed the sources. All authors contributed significantly to drafting the manuscript, revising it for important intellectual content, and approving the final version to be submitted. Each author has read and agreed to the published version of the manuscript.

Ethical consideration

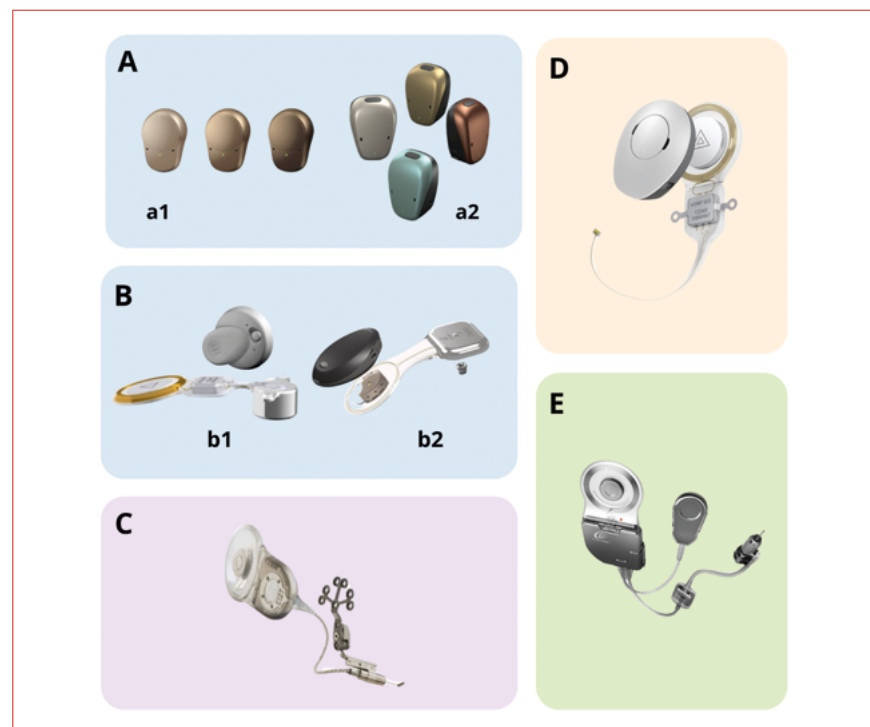
Not applicable.

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Implantable hearing aids in otosclerosis: indications, surgical applications, and cost-effectiveness



Cover figure. Implantable hearing aids used in patients affected by otosclerosis: **A)** Percutaneous bone-conduction devices; **A1)** Ponto System; **A2)** BAHA Connect; **B)** Active transcutaneous bone-conduction devices; **B1)** Bonebridge; **B2)** Osia2; **C)** Codacs; **D)** Vibrant Soundbridge; **E)** Carina.

Summary

Since the 1980s, implantable hearing devices have revolutionised otologic surgery, providing new options for patients with otosclerosis. This article discusses two primary types of devices that are beneficial to patients with otosclerosis: bone anchored hearing devices (BAHDs) and active middle ear implants (AMEIs). BAHDs include percutaneous, passive, and active transcutaneous devices, offering an alternative for patients where stapes surgery or conventional hearing aids are not feasible. Although BAHDs improve audiological outcomes, they are generally considered a third-line treatment due to their limited cost-effectiveness ratio in otosclerosis. AMEIs, such as the Vibrant Soundbridge, are another option, offering superior speech recognition without the occlusion effects of traditional hearing aids. While implantable hearing devices show promising results, they are typically reserved for patients at high surgical risk or who do not benefit from conventional hearing aids. Further cost-benefit analysis is needed, as implantable devices are less economically favourable compared to stapes surgery.

Key words: implantable hearing devices, bone-anchored hearing aid, middle ear implants, otosclerosis

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Introduction

Since the mid-1980s ¹, otologic surgery has been revolutionised by the advent of implantable prostheses, which have modernised the approach to hearing rehabilitation in patients with otologic issues.

Since then, numerous prostheses with different characteristics have been developed to address the hearing deficit of patients. Among these, only some are indicated and have been used in patients affected by otosclerosis:

- bone anchored hearing devices (BAHDs);
- active middle ear implants (AMEIs).

The aim of this paper is to clarify indications and surgical applications of implantable hearing aids in patients affected by otosclerosis (Cover figure).

Bone anchored hearing devices

The first to have been developed are bone-anchored prostheses. The use of penetrating implants was initially described in 1977 ¹, but it was a further 10 years before the devices became commercially available. At present, the BAHDs available are:

- percutaneous bone-conduction devices such as the Baha Connect (Cochlear BAS, Gothenburg, Sweden) and the Ponto System (Oticon Medical AB, Askim, Sweden). These involve a titanium screw implanted in the skull bone, protruding through the skin to which an external audio processor is attached;
- passive transcutaneous bone-conduction devices such as the Baha Attract (Cochlear BAS, Gothenburg, Sweden) and Sophono (Medtronic, Jacksonville, FL). These devices do not penetrate the skin but use magnetic coupling to transmit sound from processor to the bone where the magnet is attached. The sound vibration passes through the skin;
- active transcutaneous bone-conduction devices such as the Bonebridge (MED-EL, Innsbruck, Austria) and Osia ² (Cochlear BAS, Gothenburg, Sweden), in which an active implant (with magnetic or piezoelectric transducer) is placed under the skin and muscles of the temporal region and communicates with the external sound processor wirelessly via radiofrequency.

These devices have been widely used in patients affected by otosclerosis ^{2,3}; however, they are considered only as a third option in the treatment of hearing loss ².

Studies have shown the benefits of BAHDs in terms of audiological performance and overall patient quality of life ^{4,6}, even in patients affected by otosclerosis, although the benefits are slightly less pronounced compared to patients with other middle ear pathologies ³.

As most recent paper underlines ^{7,8}, these devices are recommended only in cases of surgical failure, or in cases in which a surgical revision exposes the patient to a high risk of deafness and conventional hearing aids cannot be fitted. The Brazilian task force on otosclerosis ⁷ considers the main indications of BAHDs as:

- eczematous otitis externa precluding the use of conventional hearing aids or no adequate gain obtained with the device;
- unfavourable surgical anatomy (persistent stapedial artery, obliteration of the oval window by a dehiscent facial nerve);
- otosclerosis in single-sided deafness;
- revision surgery.

Some authors have also focused attention on the progressive pattern of otosclerosis and the risk of deterioration of cochlear reserve over the years, highlighting the possibility that BAHDs may no longer achieve the appropriate auditory performance ⁷.

In an evolving era of healthcare management, it is wise to reflect on the value of therapies to ensure high-quality care reaches all those who need it, avoiding useless treatments or those with an unfavourable cost-benefit ratio. In the literature, there are no studies analysing the issue of cost-effectiveness of BAHDs in the subgroup of patients with otosclerosis. However, there are studies ⁹ that have shown that stapes surgery is less expensive than treating patients with conventional hearing aids. Gillard et al. ¹⁰ assert that stapes surgery represents a beneficial and cost-effective strategy to treat otosclerosis, as it enhances quality of life while reducing expenses. Other authors ¹¹ indicate that the cost-effectiveness of BAHDs compared to conventional hearing aid devices in all types of patients remains uncertain. Considering the high cost of the devices, the cost-effectiveness ratio is likely unfavourable in patients affected by otosclerosis when compared to the other 2 options (conventional hearing aids and stapes surgery). However, further studies on cost-benefit should be carried out to clarify the ratio between BAHDs, conventional hearing aid, and stapes surgery.

Active middle ear implants

AMEIs emerged in the 1990s as a treatment option for patients who are unable to use hearing aids. They offer functional gain with improved speech recognition that surpasses that of conventional hearing aids, and most do so without causing occlusion effect or feedback. There are two main groups of AMEIs: semi-implantable (siAMEI) or fully-implantable (fiAMEI).

In patients affected by otosclerosis, there are 3 implants that have been mostly used: the Vibrant Soundbridge (VSB, Med-El, Innsbruck, Austria) and Codacs (Cochlear Ltd., Sydney, Australia) in the siAMEI group, and Carina (Cochlear Ltd., Sydney, Australia) in the fiAMEI. Currently, the only AMEI still available is the Vibrant Soundbridge.

The VSB is made by 2 components: an external sound processor and an internal part called vibrating ossicular replacement prosthesis (VORP)^{12,13}. The external component consists of a microphone, audio processor, battery, transmitter, and magnet. It converts acoustic signals into an amplitude-modulated signal and transmits them via electromagnetic waves to the VORP¹³. This consists of a receiver coil, conductor link, and floating mass transducer (FMT). The FMT, the crucial component of the VSB, contains an electromagnetic coil within a titanium housing that encloses a small magnet. When it is connected to a moving structure (ossicles, round or oval window), these vibrations can be transmitted to stimulate the fluids of the inner ear.

The VSB may be indicated in patients suffering from otosclerosis with stable hearing loss for at least 12 months. In patients with conductive hearing loss who do not adapt to or gain little benefit from conventional hearing aids and are unwilling to accept the risks of stapedotomy, the FMT can be placed on the short process of the incus using a titanium clip⁷. For patients with moderate to severe mixed hearing loss, the VSB can also be placed during or after stapes surgery^{7,8,14}. This indication is the only one taken into consideration in an Italian consensus⁸ even though this was strongly debated among the authors.

Codacs is an implantable hearing system, first reported by Hausler in 2008¹⁵, which directly stimulates the inner ear by vibrating the perilymph. The Codacs system comprises an implantable part, consisting of a receiver coil, the implant electronics, and the electromagnetic actuator, which is held in place by a fixation system, and an externally behind-the-ear sound processor with a radio-frequency coil. The actuator has a terminal – referred to as the ‘artificial incus’ – which is similar in size to the long process of the incus. The artificial incus should be positioned in such a way that it is aligned to the level of the natural incus, above the oval window, while avoiding contact with the surrounding tissues and bony structures. After positioning the artificial incus by posterior tympanotomy¹⁵ or superior-anterior tympanotomy¹⁶, a traditional stapes prosthesis is inserted into the footplate perforation and secured to the long process of the artificial incus of the actuator by crimping. The actuator transforms electrical signal into mechanical vibrations and stimulate the cochlea by applying a vibration to the stapes

prosthesis through the artificial incus bypassing the outer and middle ear. The indication range of the device is a bone conduction threshold between 40 and 80 dB (0.5–4 kHz) and an air conduction threshold higher than 60 dB. Results reported in the literature are good. Busch et al.¹⁷, in a series of 10 patients, reported an average functional gain (0.5–4 kHz) achieved with conventional hearing aids of 47 dB, compared to 56 dB with Codacs. Hausler et al.¹⁵ reported, in a case series of 4 patients, a decrease of air bone gap by 10–25 dB at pure tone audiometry.

Carina is a fully implantable hearing aid; it comprises a microphone, rechargeable battery, magnet, sound processor, actuator, and transducer. The transducer is positioned on the body of the incus. Furthermore, the Carina system features an external charger that utilises magnetic contact for device charging, along with a remote control to adjust volume and power settings. There are no visible external components, thereby resolving many of the problems (such as swimming, sports activities, and dusty work environments) related to the use of external acoustic processors. Carina is designed to address the amplification needs of adults, > 18 years of age, with moderate to severe sensorineural hearing loss and normal middle ears, providing a mechanical direct stimulation of the middle ear ossicles. However, over the years the development of extension of the actuator allowed to broaden the surgical indications. With these extensions the actuator could be positioned on middle ear: stapes, oval window, or round window. Literature reports on patients with otosclerosis undergoing Carina implantation are anecdotal^{18–20} and all patients are implanted on oval window and following multiple surgeries for otosclerosis.

Conclusions

Currently, the only implantable hearing aids for patients with otosclerosis are bone-anchored hearing aids and the VSB. The use of these devices in patients affected by otosclerosis represents a third-line therapeutic option for those at high surgical risk for stapes surgery, and in cases in which there is no indication for conventional hearing aids. Implantable prostheses can achieve good auditory outcomes; however, due to their unfavourable cost-benefit ratio they should be reserved for highly selected cases.

Conflict of interest statement

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ADV, LB, FF: conceived the initial idea for the narrative review and developed the structure of the article; SB: performed the literature review and critically analyzed the sources. All authors contributed significantly to drafting the manuscript, revising it for important intellectual content, and approving the final version to be submitted. Each author has read and agreed to the published version of the manuscript.

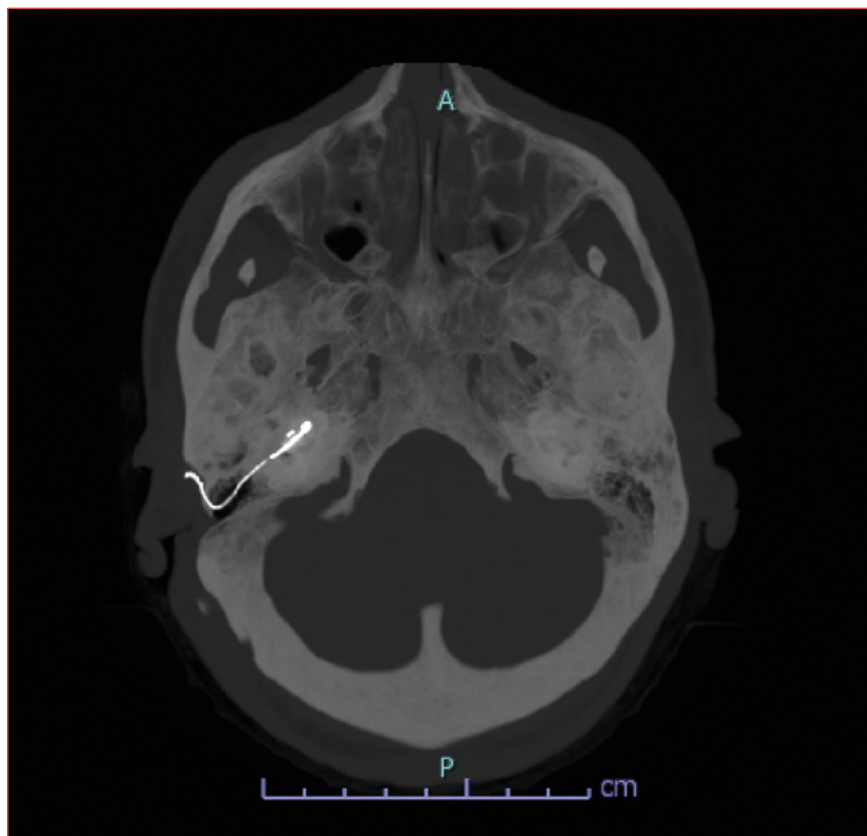
Ethical consideration

Not applicable.

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Surgical options for advanced otosclerosis



Cover figure. Axial CT of a patient with advanced otosclerosis, showing a right cochlear implant in situ.

Summary

Objective. Management of advanced otosclerosis (AO) has evolved over the past 20 years with the availability of cochlear implant (CI) in addition to stapes surgery. Both procedures are reliable treatment options for AO with similar success rates and currently there are no standard guidelines regarding the surgical treatment of AO. The aim of this paper is to report the outcomes and complications of a series of patients with AO submitted to CI at our Institution. An extensive review of the literature is also provided.

Methods. The study group was composed of 31 adult patients affected by AO, consecutively submitted to CI at our Institution. Postoperative results and complications were compared to those of a homogeneous control group of adult implanted patients, affected by post-verbal sensorineural hearing loss due to other aetiologies.

Results. Patients in both groups achieved satisfactory results in terms of speech perception in

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quiet and with background noise after CI, without no significant differences. The rate of complications in the study group was 15%, which is similar to literature reports.

Conclusions. In patients with AO, the decision between stapes surgery and CI must be personalised and well-considered, taking into account the individual characteristics of the patient and the potential risks and benefits of each option.

Key words: advanced otosclerosis, cochlear implantation, stapes surgery, hearing loss rehabilitation, surgical outcomes

Introduction

Otosclerosis is a well-known disorder of bone metabolism within the otic capsule. Most patients have conductive hearing loss (HL) and can clearly benefit from stapes surgery. However, a smaller proportion of patients, between 8.9 and 34%, eventually progress to mixed or sensorineural HL (SNHL) ¹. House and Sheehy, in 1961, first introduced the term “far advanced otosclerosis” (FAO) to describe patients with absent bone conduction thresholds and air conduction thresholds over 85 dB HL ². Iurato and colleagues added the “very far advanced otosclerosis” terminology to include those with a “blank audiogram” or immeasurable air and bone conduction thresholds ³. With improvements in audiometric equipment, the definition has changed and currently there is not a clear consensus on the definition to be used. Nowadays, in the era of cochlear implantation (CI), speech discrimination scores are more likely to be used instead of pure-tone thresholds values in the definition of the disease and Lachance et al. used the definition of FAO for cases with otosclerosis and poor discrimination scores ⁴. Similarly, other authors introduced the term advanced otosclerosis (AO) when referring to otosclerotic patients with SNHL and diminished speech discrimination scores, which falls within the criteria for CI candidacy ^{1,5}.

There are no standard guidelines regarding the rehabilitation of AO: the possible treatment options are no intervention and use of hearing aids (HA), stapedotomy and use of HA, or CI procedure. Each has its advantages, disadvantages, success rates, and complications ^{4,6-12}.

In this paper, we report the results and complications rate of a series of patients with AO submitted to CI procedure at our Institution. The results and complications will be compared to those of a homogeneous control group of adult implanted patients, affected by post-verbal SNHL due to other aetiologies. An extensive review of the literature will also be provided.

Materials and methods

The study group was composed of 31 adult patients affected by AO, consecutively submitted to CI at our Institution, during the period 1998-2022. Patients enrolled in the study gave their informed consent to participate.

Preoperatively all patients were submitted to a comprehensive audiological evaluation, including medical personal and familial history report, otomicroscopy, pure tone audiometry for air and bone conduction thresholds, impedance audiometry and stapedia reflexes study, speech audiometry, free field warble tone and speech audiometry with and without HA, and a speech perception test ¹³ without lipreading with HA in quiet and with background noise (signal to noise ratio +10). Patients were also submitted to neuroradiological evaluation using temporal bone high resolution computed tomography (CT) and brain and inner ear magnetic resonance (MR) with contrast. We defined CT findings indicative of otosclerosis as follows: obliterative otosclerosis was identified by ossification of the basal turn of the cochlea, while non-obliterative otosclerosis was characterised by the presence of otospongiotic foci, with the cochlear lumen remaining normal.

Postoperatively, during follow-up visits, all patients were assessed in the usual listening condition by warble tone audiometry in free field and a speech perception test ¹³ without lipreading in quiet and with background noise (signal to noise ratio +10). The usual listening condition could be with one CI, with bimodal stimulation or with bilateral CI, according to the devices used.

Pure tone audiometry was conducted with the Interacoustics Clinical Audiometer AC40. When measuring the hearing threshold both without and with HA, we assigned a value of 125 dB to any frequency threshold over the maximum output limit of the audiometer (105 dB for 0.25 kHz and 125 dB for 0.5 and 1 kHz, 120 dB for 2 kHz). Any vibrotactile sensation was also excluded.

Speech perception was assessed using a speech perception test in Italian language ¹³ both before (with HA) and after implantation (in the usual listening condition) in free field, by the same speech therapist in all the patients to avoid bias, with live voice, without lip reading. We evaluated the disyllabic words recognition score using lists of 20 disyllabic Italian words at a level of 65 dB. Performing the test with background noise, we used a signal to noise ratio of +10.

We compared the results of the study group to those of a control group comprising 31 adult patients with post-verbal SNHL from aetiologies other than otosclerosis. These patients received CI at our Institution and were routinely

evaluated during follow-up visits. The control group was selected based on the following criteria: age between 39 and 79 years, implanted between 1998 and 2022, normal cochlear anatomy, and absence of cognitive impairment or neuropsychiatric disorders. To ensure the control group had the same age distribution as the study group, we used random selection with SPSS software.

We correlated the speech perception results in quiet and with background noise between study and control groups, both pre- and postoperatively. We also checked if postoperative speech perception results of the study group were correlated with the previous execution of stapedoplasty in the implanted ear, the presence of basal turn ossification due to otospongiosis, electrical stimulation of facial nerve after CI activation and incomplete electrode insertion. Finally, we compared the rate of postoperative complications between the two groups.

Statistical analysis

The normality of the quantitative data was assessed using the Shapiro-Wilk test. As the data did not follow a normal distribution, differences in means were evaluated using the non-parametric Mann-Whitney U test for independent samples. Correlations between continuous, categorical, and dichotomous variables were analysed using the Spearman rank correlation coefficient or the Point-Biserial correlation coefficient. The distribution of quantitative variables across groups was examined using the Independent-Samples Kruskal-Wallis test. For testing the distribution of categorical variables, the Chi-Square or Fisher's Exact test was used as appropriate. All statistical analyses were conducted using SPSS (IBM SPSS Statistics 26, IBM, New York, NY), with a p value ≤ 0.05 considered as statistically significant.

Results

The study group was composed of 31 patients (33 implants), 18 females and 13 males, with a mean age at implantation of 65.3 years (range, 39-79). The implants used were Cochlear Nucleus CI 24 M in one patient, Cochlear Nucleus CI24RE (CA) in 4, Cochlear Nucleus CI512 in 20, and Cochlear Nucleus CI612 in 7. We used a straight array in one patient implanted at the beginning of our series, when perimodiolar electrodes were not available.

We performed a unilateral CI in 29 patients and a sequential bilateral CI in 2. Ten unilaterally implanted patients use the bimodal stimulation. Fourteen patients had previously undergone stapes surgery in the implanted ear.

Preoperative CT showed an obliterative otosclerosis in 16 ears. Preoperatively the mean disyllabic words recognition

score with hearing aids was 30.6% (range, 0-100%) in quiet and 11.7% (range, 0-70%) with background noise. The mean follow-up after surgery was 8.5 years (range, 1-24).

The control group was composed of 31 patients (32 implants), 19 females and 12 males, with a mean age at implantation of 65.1 years (range, 39-79). The implants used were Cochlear Nucleus CI 24 M in one patient, Cochlear Nucleus CI24RE (CA) in 6, Cochlear Nucleus CI512 in 20, and Cochlear Nucleus CI612 in 4 patients (bilateral CI in one patient). We performed a unilateral CI in 30 patients and a sequential bilateral CI in one patient. Ten unilaterally implanted patients use the bimodal stimulation. All the procedures, both for the study and control groups, were performed by the same senior surgeon.

Preoperatively, in the control group the mean disyllabic words recognition score with hearing aids was 23.7% (range, 0-65%) in quiet and 6.6% (range, 0-35%) with background noise. The mean follow-up after surgery was 6.3 years (range, 1-17). No statistically significant difference in preoperative speech recognition scores was present between the study and the control group. Postoperatively in the study group the mean disyllabic words recognition score in the usual listening condition was 69.4% (range, 30-100%) in quiet and 45.7% (range, 0-95%) with background noise. The usual listening condition was with one CI for 19 patients, with bimodal stimulation for 10, and with bilateral CI for 2.

Postoperatively in the control group the mean disyllabic words recognition score in the usual listening condition was 77.7% (range, 50-100%) in quiet and 42.5% (range, 0-85%) with background noise. The usual listening condition was with one CI for 20 patients, with bimodal stimulation for 10, and with bilateral CI for one (Fig. 1).

With regards to complications, in the study group we recorded an incomplete insertion of the array in 2 ears (6%), and a mild gusher that spontaneously resolved intraoperatively in one ear (3%); in no case was there misplacement of the electrode array. Due to postoperative facial nerve stimulation (FNS), it was necessary to modify the implant fitting and to exclude some electrodes in 7 ears. In 2 patients, the fitting changes and the number of excluded electrodes caused a reduction of the outcome. We included only these 2 patients in the calculation of complications (6%). The rate of complications in the study group was 15%. In one patient the electrode array was inserted in the scala vestibuli, due to the obliteration of the scala tympani lumen; this was not included among the complications, as the scala vestibule insertion did not affect the results.

In the control group there was no misplacement or incomplete insertion of the electrode array, gusher, or FNS. There

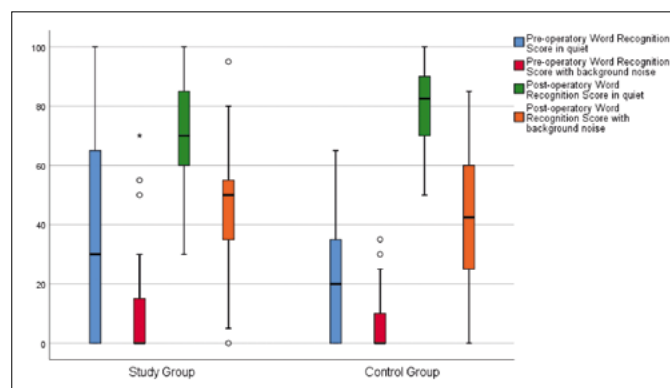


Figure 1. The boxplot shows words recognition scores, both in quiet and with background noise, before and after cochlear implantation in the study and control groups. Circles define outliers, while an asterisk marks a large outlier.

were also no significant differences in postoperative speech perception in quiet and with background noise between the study and control groups.

Within the study group, we found no significant correlation between postoperative word recognition scores, both in quiet and with background noise, and prior stapes surgery, presence of obliterative otosclerosis, and incomplete insertion of the array or FNS.

In Table I the main clinical and audiological features of the patients belonging to the study and control group are reported.

Discussion

Management of AO has evolved over the past 20 years with the availability of CI in addition to stapes surgery ⁶. Both stapes surgery and CI are reliable treatment options for AO with similar success rates and, currently, there are no standard guidelines regarding the surgical treatment of AO.

In the choice between stapes surgery and CI, the success rate is not the only factor to play a role in the decision; each intervention has specific advantages and disadvantages. Furthermore, many factors must be taken into account besides the audiogram and the air bone gap, such as imaging, contralateral ear hearing level, duration of HL, economic issues, and patient's preference.

Stapedotomy is a relatively simple, safe, and cost-effective procedure that can accomplish very good results in patients experiencing severe to profound HL due to otosclerosis, who are potentially candidates for CI ^{4,7,8}. In 2014, Van Loon published a systematic review and meta-analysis on stapedotomy in patients with FAO, finding that combining stapedotomy with hearing aid fitting led to good outcomes in a

significant number of cases, with 35% of patients achieving a postoperative speech perception score exceeding 80% ⁷. They also showed that, in comparison to CI procedure, stapes surgery is reportedly less expensive, less complex as it does not need a postoperative rehabilitation programme and offers a more natural quality of sound, allowing a better appreciation of music. Finally, these authors highlighted that stapedotomy can be easily performed under local anaesthesia, making the procedure especially applicable for the elderly and patients with comorbidities ⁷. However, a feared complication of stapedotomy is an increase of SNHL, which in AO could result in a functionally deaf ear ⁴.

According to these reasons, some authors suggest considering stapes surgery as the first surgical option in patients with AO, and to reserve CI for cases of failure ^{7,8}.

However, the results after stapedotomy in severe mixed HL are variable and unpredictable. In 2004, our group published the results of 8 patients with FAO submitted to stapes surgery: the results were quite variable, which were satisfactory in 5 patients and poor in the remaining 3 ⁶.

Although stapedotomy in otosclerosis can achieve a stable long-term hearing improvement, patients with otosclerosis may demonstrate a further progression of SNHL that cannot be explained by age alone and that may affect the long-term results after stapedotomy. To date, the exact rate of this progression remains unclear, emphasising the need for studies with longer follow-up after stapedotomy in patients with FAO ⁷. In this regard, the effects of stapedotomy reported in the literature and reviews are predominantly based on a single postoperative measurement, and most studies lack long-term follow-up ^{6,8}. Four of 8 patients with FAO submitted to stapedotomy, and reported in the above mentioned study ⁶, during long-term follow-up experienced deterioration of the results and were subsequently submitted to CI (unpublished data).

There are no reportedly reliable prognostic factors for the results after stapedotomy in patients with AO. Age, gender, preoperative pure tone audiometry, and preoperative speech recognition scores do not seem to predict outcomes after stapedotomy ⁷. Also, the pericochlear extent of otospongiotic foci as seen on preoperative high-resolution CT does not seem to be correlated with postoperative audiologic performance ⁷.

CI is currently the gold standard for rehabilitation of severe to profound HL and has also been shown to be effective for patients with AO. Historically, the application of a CI to otosclerotic patients was initially met with skepticism, and FAO was considered a contraindication to implant candidacy; nevertheless, in recent years, a growing body of evi-

Table 1. Clinical and audiological features of the study and control group, and outcomes. A statistical comparison between the two groups is provided.

	Study group	Control group	p value
N	31 (33 CI)	31 (32 CI)	
F/M ratio	18/13	19/12	0.739136
Age (years)	65.3 (range, 39-79)	65.1 (range, 39-79)	0.915887
Unilateral/bilateral CI	29/2	30/1	0.711332
Bimodal users	10/29	10/30	0.244659
Follow-up (years)	8.5 (range, 1-24)	6.3 (range, 1-17)	0.058833
Preop WRS in quiet	30.6% (range, 0-100%)	23.7% (range, 0-65%)	0.004355*
Preop WRS with background noise	11.7% (range, 0-70%)	6.6% (range, 0-35%)	0.133715
Complications	5/33 (15%)	0/32 (0%)	0.0531
Postoperative WRS in quiet	69.4% (range, 30-100%)	77.7% (range, 50-100%)	0.161134
Postoperative WRS with background noise	45.7% (range, 0-95%)	42.5% (range, 0-85%)	0.664712

WRS: words recognition score; * indicates statistically significant difference.

dence supports the notion that CI is safe and beneficial in AO.

Unlike stapes surgery, CI is an expensive and complex procedure; in the case of otosclerotic patients, it requires experienced surgeons and audiologists, and advanced otosclerosis poses a unique challenge to both the implant team and the patient¹⁰. Intraoperatively, distorted bony anatomy from ossification may necessitate extra-drilling and trauma to the cochlea, and cochlear demineralisation and obliteration may result in the incomplete insertion or misplacement of the electrode array. In this regard, the surgical facility for management of cochlear obstruction and altered bony anatomy is crucial¹. Postoperative complications can develop as a result of the altered current distribution of remodelled bone, leading to higher rates of non-auditory stimulation, mainly FNS¹⁰⁻¹². For these reasons, comprehensive preoperative counselling to discuss the multiple modalities for hearing rehabilitation in AO, including CI, as well as the expected results and possible difficulties is needed^{1,11}.

In the last few years, a number of review articles and meta-analyses have been published on CI in patients with otosclerosis. It is reported that patients with AO who undergo CI commonly achieve satisfactory speech perception benefits^{10,12}. Also, the subjectively perceived benefits after implantation, evaluated by patient-reported outcome measures (PROMs) are good, with no significant differences in comparison to patients with different aetiologies of HL^{11,14}. Lam et al., in a systematic review on this topic, concluded that the hearing outcomes after CI in otosclerosis are generally good, with the majority of patients experiencing good

audiometric outcomes and PROMs at 12 months after implantation¹¹. A systematic review by Kondo et al. reported similar results: they showed improvements in speech recognition scores from CI in patients with FAO similar to general adult CI outcomes¹⁰.

In our aforementioned clinical study, we submitted 5 patients with FAO to CI procedure: in all patients we obtained satisfactory hearing and speech perception results, and 4 of 5 patients were able to have telephone conversations⁶.

Conversely, in a clinical study by Wong et al., patients with AO achieved slightly poorer speech perception scores after CI than a control group of non-otosclerotic patients, but the difference between groups was not significant¹⁵.

In agreement with the majority of literature data, the current study found that both the study and control groups achieved satisfactory results in terms of speech perception in quiet and with background noise after CI. Furthermore, outcomes for otosclerotic patients did not differ significantly from those of control patients with HL due to other aetiologies. Despite generally good hearing and speech perception results, otosclerosis patients undergoing CI report a higher frequency of surgical issues, as well as intra- and postoperative complications. Lam et al., in their paper, noted that a small but significant portion of patients experience poor outcomes post-implantation, often associated with postoperative complications such as FNS¹¹. Similarly, Kondo et al. reported that otosclerotic patients have higher than usual rates of FNS and partial insertions¹⁰.

Diversity of cochlear anatomy due to ossification should be kept in mind and surgeons need to be prepared for the

possibility of obstacles during insertion and the need for an alternative insertion scenario during the procedure¹⁶. The rate of incomplete insertions in patients with AO is about 10% and is higher than what is generally found in implanted adult patients (2%)¹⁰. Although the difficulty of electrode insertion in otosclerosis is often attributed to ossification of the basal turn, a histopathological analysis by Lee et al. showed that cases of partial insertion were associated with cochlear lumen obstruction in only a small number of cases¹⁷. In most cases, cochlear obstruction can be by-passed with the drilling of the basal turn, thus enabling full insertion of the array. Alternatively, for more extended obstructions, scala vestibuli implantation can be a viable option¹⁸. In the literature it has been utilised to variable extents, with the upper limit being in 21% of patients treated by Kabbara et al.^{10,19}. In cases of scala vestibuli array insertion, most authors did not find any significant difference in postoperative audiological outcomes between scala vestibuli and scala tympani electrode insertions^{15,18}, although previous studies have shown that full electrode insertions into the scala tympani are associated with superior speech perception²⁰. In one of the patients of the present study group, a scala vestibuli insertion was executed due to the severity of scala tympany ossification. No significant impact on the postoperative result was recorded¹⁷.

A major concern regarding CI in otosclerotic patients is the possibility of FNS, which is reportedly higher than in the general population of implanted patients^{10,12,21,22}; in the review by Kondo et al., FNS was the most common non-auditory stimulation and was reported in 18% the cases, which is higher than the 6% rate reported across reviews for all adult CI patients¹⁰. The mechanism underlying this phenomenon seems to be related to the reduced impedance of the otic capsule, which causes electrical currents to shunt through the bone. This leads to an increased current requirement to stimulate auditory nerve fibres and a potential excess current spread to the facial nerve, causing FNS¹⁰. This phenomenon requires to be managed with more frequent adjustments of the electrical map and proper follow-up, with the need to switch off some electrodes, reportedly typically 1-2, but in some cases up to 8, potentially leading to a decrease in the auditory results. Despite this, Kondo et al. reported that studies comparing speech perception outcomes between patients with and without otosclerosis showed poorer results for the former group, but without reaching statistical significance¹⁰. Some authors report that a reduction in audiological outcomes may be correlated with number of electrodes deactivated, but this

relationship has yet to be clarified²³. It has been hypothesised that speech perception has an inverse exponential decay relationship to electrode deactivation, such that there is a threshold of stimulation. For instance, significant deterioration in speech perception is seen with a higher number of electrodes deactivated whereas it has not been observed with a smaller number^{24,25}. Nevertheless, a recent study by Atanasova-Koch et al. also noted that deactivated electrodes did not make a significant difference in speech differentiation²³.

Finally, some studies have suggested the benefit of using perimodiolar electrodes to achieve lower rates of FNS¹⁰; it is estimated that with perimodiolar electrodes, the rate of FNS dropped to nearly 0%^{10,12}.

Another issue concerning CI procedure in otosclerotic patients is the possibility of progressively decreased performance. This decrease in performance over time can be attributed to several factors, including the unique anatomical and pathological challenges presented by otosclerosis. Some patients may experience a decline in speech recognition scores over time, potentially due to ongoing cochlear changes or suboptimal electrode positioning and insertion depth necessitated by the ossified cochlear structures. The progressive nature of otosclerosis itself can lead to further ossification within the cochlea after implantation. This can impair the performance of the implant due to changes in cochlear structure that affect the transmission of electrical signals from the implant to the auditory nerve. Additionally, there is evidence that otosclerotic patients may experience non-auditory stimulation and FNS more frequently than other cochlear implant users, which can contribute to decreased auditory performance and user discomfort²⁶.

Structural changes in bone may be progressive, potentially affecting stimulation thresholds, electric charges, pulse widths, stimulation rates, and ultimately, the number of active electrodes, leading to a decrease in outcomes. However, this aspect is not clearly reported in the literature²⁶. Despite electrode switch-off due to FNS and higher partial insertion rates, CI in AO is generally reported to have comparable speech discrimination rates to normal adult CI^{10,12,14}.

With regards to other complications, a higher incidence of gusher and lower frequency of postoperative vertigo are reported in this group of patients¹⁰. In our study group, otosclerotic patients had a low rate of complications of 15%, consistent with other literature reports^{9,10}, even though when compared to the control group, otosclerotic patients had a higher rate of complications. We had incomplete electrode insertion in 6% of otosclerotic patients, which is lower than the percentage reported by Kondo et al. in 2022¹⁰.

We observed a gusher in 3% of cases and FNS affecting results in 6% of cases. This is lower than the 18% reported by Kondo et al., possibly due to different criteria for considering FNS as a complication; in fact, we included only cases where FNS reduced speech perception. Furthermore, we used a perimodiolar electrode in a very high proportion of patients, which could explain the low FNS rate.

Teaima et al. in 2023 published an interesting review article, comparing outcomes and side effects in patients with FAO submitted to stapes surgery and CI procedure⁹, concluding that results and complications of CI and stapes surgery in FAO patients are different. In most of the studies included in the review, CI was considered highly favourable and more recommended than stapes surgery, while other studies showed no significant difference in postoperative outcomes: CI had a reportedly better mean PTA than stapes surgery and a significantly higher mean for recognition of phrases. On the other hand, stapes surgery had a higher mean for recognition of monosyllables and disyllables than CI⁹. With regards to side effects, including dysgeusia and tinnitus, the review showed that postoperative complications were significantly lower in CI (13.6%) than stapes surgery (18.6%). However, vertigo was lower in stapes surgery than in CI. Finally, CI had a significantly lower rate of revision surgery than stapes surgery⁹.

Radiological assessment of the severity of otosclerosis has a vital role in preoperative planning, as it may predict difficulties in positioning the electrode or the risk of incomplete insertion, but its value in predicting postoperative hearing outcomes is controversial^{11,15}. Wong et al. conducted a retrospective study on the role of preoperative radiological assessment of the petrous bone and found that narrowing or signal change in the cochlear lumen has a significant effect on the final electrode position, whereas round window ossification or obstruction did not seem to be relevant¹⁵. Furthermore, they found a strong correlation between preoperative imaging and intraoperative findings for both the cochlea and round window. However, in their study they found that the correlation between postoperative electrode position and preoperative imaging was moderate¹⁵. In addition, they found no significant correlation between hearing outcomes and preoperative radiology, intraoperative findings or postoperative electrode position, concluding that preoperative imaging findings do not predict postoperative speech perception outcomes¹⁵. Similarly, in the current study, we did not find a significant correlation between the evidence of obliterative otosclerosis at preoperative CT and the results after implantation.

Conclusions

The current surgical options for AO include stapes surgery and CI. Unfortunately, to date, there are no universally accepted guidelines to determine the most suitable option for each patient, and a universally recognised definition of this condition is also lacking, making it difficult to compare the results across different studies in the literature. The surgical choice should be guided not only by the patient's audiological profile and the presence and extent of the air-bone gap, but also by the level of speech discrimination, imaging results, and, secondarily, by the patient's age, economic factors, hearing in the contralateral ear, and preference after thorough counselling. Both procedures present specific advantages and issues. Stapes surgery yields more variable and less predictable results and reportedly carries a higher rate of side effects. On the other hand, CI generally provides satisfactory outcomes, in most studies not significantly different from those of adult CI recipients with other aetiologies, but it is a more complex and expensive procedure and can present surgical and postoperative issues that may be challenging for both surgeons and the CI team. These challenges can include partial or incorrect insertion of the electrode array and the possibility of intraoperative gusher. Postoperatively, electrical FNS is a significant concern, potentially affecting outcomes, which must be managed by an experienced team; additionally, mapping difficulties can arise, and there is ongoing debate about the potential for progressive deterioration of results. All these aspects must be thoroughly discussed with the patient in a detailed preoperative counselling. In conclusion, the decision between stapedoplasty and CI must be personalised and well-considered, taking into account the individual characteristics of the patient and the potential risks and benefits of each option. Further comparative studies and detailed guidelines are desirable to provide clearer indications and support clinicians in therapeutic decision-making.

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

SB, FF, LB: conceived the initial idea for the narrative review and developed the structure of the article; LDG, SC, DB, FL: performed the literature review and critically ana-

lyzed the sources. All authors contributed significantly to drafting the manuscript, revising it for important intellectual content, and approving the final version to be submitted. Each author has read and agreed to the published version of the manuscript.

Ethical consideration

Not applicable.

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Stapes revision surgery: intraoperative findings and audiological results. A multicentric study



Cover figure. Axial CT scan showing left-sided displacement of a metallic stapes prosthesis in a patient previously submitted to stapedoplasty.

Summary

Objective. To explore the results of revision stapes surgery within a multicentric cohort, focusing on hearing improvements and correlation with the type of postoperative hearing loss experienced and related findings during the revision procedure.

Methods. A retrospective study of 308 consecutive revision stapes surgeries performed by 5 Otorhinolaryngologic Units in Pisa, Turin, Pavia, Piacenza, and Rome between 2010 and 2023 was accomplished.

Results. The most frequent causes leading to revision stapes surgery were prosthesis dislocation (56.1%), use of a short prosthesis during primary surgery (13.9%), and an eroded incus (17.2%). The median air conduction threshold significantly improved after revision surgery, while the bone conduction threshold remained stable.

Conclusions. Revision stapes surgery effectively improves hearing in patients with unsuccessful initial operations, with a significant reduction in the air-bone gap (ABG). The audiological results in our patients are favourable. ABG closure within 10 dB was achieved in 57.2% of cases and within 20 dB in 76% of cases. Stapes revision surgery is feasible and provides an acceptable success rate.

Key words: revision stapes surgery, hearing loss, otosclerosis, prosthesis dislocation, incus erosion

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Introduction

Since the mid-20th century, surgical intervention has been the standard treatment for otosclerosis-related hearing impairment¹. Stapes surgery is effective in reducing the air-bone gap (ABG) to less than 10 dB in nearly 90% of cases². However, some authors have pointed out that up to 20% of patients may require a second surgery due to persistent or recurrent hearing loss or vertigo³⁻⁷. Immediate failures leading to continued hearing loss can arise from issues such as improper placement of the prosthesis or other causes like superior semicircular canal dehiscence or ossicular chain problems⁸. On the other hand, delayed failures, presenting as either gradual or sudden recurrence of hearing loss, can be due to reasons such as prosthesis dislocation, erosion of the incus, regrowth of the footplate, or scarring⁸.

Revision operations for otosclerosis generally yield less favourable results than primary surgery, with successful ABG reduction observed in 40% to 78% of cases during the first surgical revision and in 21% during the second revision⁹⁻¹². Revision surgery is also reported to be more frequently accompanied by complications like sensorineural hearing loss and vertigo⁹⁻¹². Moreover, the risk of deafness appears to be 5 times higher after revision surgery compared to primary surgery (0.5% or below)¹². Nevertheless, some recent studies have begun to question this trend, pointing out the variability in outcomes and the scarcity of research into the causes for revision surgery and their impact on success rates^{13,14}.

Surgery remains the preferred treatment for otosclerosis, including revision cases. Hearing aids, despite their utility, offer a lower quality of life compared to surgery and come at a higher cost¹⁵. Bone-implanted prostheses serve as a third option following surgical interventions, including stapes revision surgery and the use of conventional prostheses¹⁶.

The aim of this study was to explore the results of revision stapes surgery within a multicentric cohort. We focused on hearing improvements and their correlation with the type of postoperative hearing loss experienced and the related findings during the revision procedure. This investigation aims to provide better guidance for patients undergoing revision stapes surgery following an unsuccessful initial operation.

Materials and methods

Patients

All 308 consecutive revision stapes surgeries performed at 5 Otorhinolaryngologic Units in Pisa, Turin, Pavia, Pia-

cenza, and Rome between 2010 and 2023 were enrolled in this retrospective study. These surgeries were carried out on 283 subjects, as 15 underwent 2 revision procedures, and 5 underwent 3 revisions.

Medical charts were analysed for demographic data and medical history. The surgical report of primary surgery was reviewed to define the operative technique employed (stapedotomy or stapedectomy). Intraoperative findings during the revision surgery (e.g., erosion of the long process of the incus, perilymphatic fistula, malleus fixation) were recorded, and the data were correlated with postoperative audiological results. For patients who underwent high-resolution computed tomography (HRCT) before the revision surgery, radiological findings were evaluated and compared with intraoperative findings. Pure tone audiometry was performed pre- and postoperatively in a soundproof cabin according to the ISO 8253-1 and 8253-3 standards.

Surgical procedure

In almost all cases, the revision surgery was performed using a transcanal approach under local anaesthesia, as in primary surgery¹⁷. Only upon the patient's request, due to anxiety or other reasons, was the procedure performed under general anaesthesia. During revision surgery, the malleus and incus were visually inspected, and their mobility assessed by gentle palpation. The connection of the prosthesis to the incus or malleus and its position in the niche of the oval window were checked. Scars or bridles were gently removed with a tip; laser was used by some surgeons within our group for this purpose. No stapedectomy was reported in the primary surgery; instead, all cases involved a stapedotomy followed by placement of a piston between the incus and the platinar hole. During revision surgery, the original stapedotomy fenestra was inspected. Anatomic/pathologic irregularities of the middle ear were found in only 72 cases (23.3%). In particular, facial nerve dehiscence was described in 13 (4.2%) patients, and obliteration of the oval window in 4 (1.3%).

During revision, the causes of hearing deterioration were identified and corrected. In case of prosthesis dislocation, a new footplate hole was made using a microdrill or laser, and a new prosthesis repositioned. If the stapedial piston prosthesis was too short, it was replaced by a prosthesis of adequate length. If the incus was eroded, the new stapedial prosthesis was attached to the residual incus or fixed by performing a malleostapedioplasty. In case of perilymphatic fistula, it was sealed using autologous fat on the oval window or perichondrium. A malleostapedioplasty with section of the head was performed in cases of malleus-incus ankylosis¹⁸.

During primary surgery, 2 types of prostheses were predominantly used: platinum-Teflon in 62.3% and Teflon in 36.3% of cases. Other types of prostheses were rarely used, including nitinol (0.3%), titanium (0.3%), and titanium-Teflon (0.6%). Similarly, in revision surgery, platinum-Teflon prostheses were used in 58.4% and Teflon prostheses in 35% of cases, with other types being rarely employed: nitinol (0.6%), Teflon-titanium (4.8%), and titanium (0.6%).

Audiometric assessment

Audiometric evaluation included assessment of pre- and postoperative air-conduction (AC) thresholds (at 0.25, 0.5, 1, 2, 3, 4, and 8 kHz), bone-conduction (BC) thresholds (at 0.25, 0.5, 1, 2, 3, and 4 kHz), and ABG (at 0.5, 1, 2, and 3 kHz). Only AC and BC results obtained at 12 months after surgery were used for the calculation of the ABG and pure-tone averages (PTAs). Postoperative “dead ear” was defined as profound sensorineural hearing loss on all postoperative audiologic examinations. All patients had at least a 12-month audiological follow-up. Audiometry was reported according to the American Academy of Otolaryngology – Head and Neck Surgery guidelines¹⁹.

Statistical analysis

A descriptive analysis of all variables, including quantitative and qualitative data, was reported. The normal distribution of numerical variables was assessed using the Shapiro-Wilk test and the Kolmogorov-Smirnov test. The numerical variables were not normally distributed. Subsequently, the variables were compared using suitable statistical methods, including the Mann-Whitney U test for non-parametric data and the Chi-square test for categorical variables. The correlation between variables was determined using Spearman's rank correlation for univariate analysis and linear regression for multivariate analysis. The software used for the analysis was the SPSS version 23 (IBM Corp., Chicago, IL, USA).

Results

Patients

The cohort comprised 202 females (65.5%) and 106 males (34.5%), with a male-to-female ratio of 1:1.9. The mean age of the cohort was 52 years (± 11.5 , range 23–80). Of all surgical procedures, 283 (91.9%) were primary revisions, 20 (6.5%) were secondary revisions, and 5 (1.6%) were tertiary revisions. The indications for revision surgeries were either hearing loss or vertigo. Revision surgery was recommended in 295 cases (95.8%) for persistent or recurrent hearing loss characterised by an average ABG of 4 frequen-

cies above 20 dB, and in 9 cases (2.9%) for vertigo, imbalance, and/or signs of perilymphatic fistula. Moreover, the surgical procedure was interrupted in 4 cases (1.3%).

The surgical procedures were mostly performed under local anaesthesia (94.2% of cases) and less frequently under general anaesthesia (5.8%), according to the patient's and surgeon's preferences. Local anaesthesia was the preferred option for individuals with vertigo.

Before the revision surgery, CT was conducted in 63 subjects, constituting 20.4% of the entire study group. CT accurately identified dislocated prostheses in about half of these cases (41.2%) and a short prosthesis in 8 cases (12.6%). In the remaining instances (46.1%), scan failed to identify the underlying cause necessitating surgical revision. Therefore, the sensitivity of the test in our dataset is 53.9%, while the specificity cannot be calculated as the group lacked healthy subjects.

Intraoperative results

The causes of failure after primary surgery were intraoperatively evaluated. These findings are detailed in Table I. The most frequent causes leading to revision surgery were prosthesis dislocation (56.1%), eroded incus (17.2%), and use of a short prosthesis during primary surgery (13.9%). These 3 causes accounted for 87.2% of the reasons leading to revision in our population. In all cases, since the prosthesis was extruded from the footplate hole, it resulted in its re-ossification or closure by scar tissue.

Less frequent causes of primary surgery failure included hypomobility of the ossicular chain due to ankylosis or scar (8.4%), perilymphatic fistula (2.6%), prosthesis too long (0.3%), or interruption of the primary surgical procedure (1.3%).

The time of symptom onset after primary surgery was divided according to the surgical findings, as reported in Table I. Immediate surgical failures necessitating swift revision included a perilymphatic fistula (after 2 months) and a prosthesis that was too short (after 10 months). Conversely, other factors led to surgical revisions over a longer period, with incus erosion typically occurring after an extended period, averaging 114 months (data not shown).

The percentages of failure for the first operation, categorised by type of prosthesis used, are also presented in Table I. Prosthesis dislocation occurred in 47.4% of cases with platinum-Teflon prostheses and in 70.5% with Teflon prostheses. Incus erosion was observed in 21.3% of cases with platinum-Teflon prostheses and in approximately 10% with Teflon prostheses.

Table I. Causes of failure after primary surgery as observed intraoperatively during revision surgery.

Main cause of failure	All surgical procedure (n = 308)	Prosthesis in platinum-Teflon (n = 192)	Prosthesis in Teflon (n = 112)
Dislocated prosthesis	173 (56.1%)	91 (47.4%)	79 (70.5%)
Eroded incus	53 (17.2%)	41 (21.3%)	11 (9.8%)
Short prosthesis	43 (13.9%)	24 (12.5%)	19 (16.9%)
Long prosthesis	1 (0.3%)	1 (0.5%)	-
Malleus-incus ankylosis	6 (1.9%)	5 (2.6%)	1 (0.8%)
Scar of the ossicular chain	20 (6.4%)	18 (9.3%)	2 (1.7%)
Perilymphatic fistula	8 (2.6%)	8 (4.1%)	-
Surgery interrupted	4 (1.3%)	4 (2%)	-

Data are also grouped by the 2 more used types of prostheses in the study sample: platinum-Teflon and full Teflon; the data for the residual 4 prostheses (one in nitinol, one in titanium, and 2 in titanium-Teflon) are not reported.

Table II. Audiometric results of our series.

Stapedoplasty	Preoperative (mean SD, range in dB)	Postoperative (mean SD, range in dB)	p value
Air conduction pure tone average (0.5-3 kHz)	55.03 (± 14.57, 33.75-95)	52.57 (± 19.53, 15-100)	0.396
Bone conduction pure tone average (0.5-3 kHz)	27.82 (± 12.41, 5-70)	29.08 (± 12.86, 5-67.5)	0.264
ABG (0.5-3 kHz)	27.21 (± 9.6, 6.25-50)	23.47 (± 14.8, -3.75-56.25)	0.015
Revision surgery			
Air conduction pure tone average (0.5-3 kHz)	64.52 (± 17.02, 28.75-115)	46.30 (± 20.59, 8.75-111.25)	8.72×10^{-24}
Bone conduction pure tone average (0.5-3 kHz)	33.96 (± 14.1, 5-106.25)	32.89 (± 15.16, 8.75-111.25)	0.42
ABG (0.5-3 kHz)	30.45 (± 12.06, -1.87-66.25)	13.30 (± 12.42, 1.15-56.25)	2.52×10^{-43}

Audiometric results

The median AC and BC thresholds before stapedotomy were 55 dB and 27.8 dB, respectively. The median ABG was 27.2 dB. After stapedotomy, the median AC and BC thresholds were 52.5 dB and 29 dB, respectively. The median postoperative ABG was 23.4 dB. No statistically significant differences were found between pre- and post-stapedotomy AC and BC thresholds. However, the difference between pre- and post-stapedotomy ABG was statistically significant ($p = 0.015$).

Before revision surgery, the median AC and BC thresholds were 64.5 dB and 33.9 dB, respectively. The median pre-revision ABG was 30.4 dB. The median AC and BC thresholds after revision surgery were 46.3 dB and 32.8 dB, respectively. The median ABG was reduced to 13.3 dB. The post-revision AC thresholds were significantly better than the pre-revision ones ($p < 0.001$), without significant dif-

ferences in pre- and post-revision BC thresholds. The difference between pre- and post-revision ABG was also significant ($p < 0.001$). These data are summarised in Table II. The success of revision surgery can be expressed as the difference in ABG (Δ ABG) before and after revision surgery, excluding patients with significant post-revision BC threshold decrement. The median value of this parameter was 16.2 dB. The post-revision ABG was better than 10 dB in 57.2% of cases and better than 20 dB in 76%, with only one case of cochlear damage, which was excluded from the statistical analysis.

Univariate analysis indicated a significant negative correlation between Δ ABG and surgeries conducted under general anaesthesia (Spearman $\rho = -0.177$, $p = 0.010$). Furthermore, Δ ABG was significantly negatively correlated with the number of days of hospitalisation (Spearman $\rho = -0.372$, $p = 0.007$). Δ ABG was also positively correlated with high-

Table III. Univariate and multivariate analysis report with Δ ABG (difference in air-bone gap before and after the revision surgery) as dependent variable.

	Spearman's rho			Multivariate linear regression analysis			
	Correlation coefficient	Sig. (2-tailed)	Standardised coefficient beta	t	Sig.	95% CI - lower bound	95% CI - upper bound
Local anaesthesia "yes"	-0.177	0.010	-0.030	-1.085	0.279	-3.913	1.131
Use of laser "yes"	-0.085	0.127					
Prosthesis width	-0.147	0.087					
Prosthesis length	-0.025	0.775					
Days of hospitalisation	-0.372	0.007	0.013	0.471	0.638	-0.895	1.458
Pre-revision air conduction PTA (0.5-3 kHz)	0.234	0.001	0.797	21.823	0.000	0.589	0.706
Pre-revision bone conduction PTA (0.5-3 kHz)	-0.259	0.000	-0.574	-14.020	0.000	-0.599	-0.452
Post-revision air conduction PTA (0.5-3 kHz)	-0.527	0.000	-1.233	-27.027	0.000	-1.007	-0.870
Post-revision bone conduction PTA (0.5-3 kHz)	-0.184	0.008	0.795	16.155	0.000	0.720	0.919
Difference in months between primary surgery and revision	0.0878	0.328					

er pre-revision AC PTA (Spearman $\rho = 0.234$, $p = 0.001$) and negatively correlated with higher pre-revision BC PTA (Spearman $\rho = -0.259$, $p < 0.001$). Δ ABG was also negatively correlated with post-revision AC PTA (Spearman $\rho = -0.527$, $p < 0.001$) and post-revision BC PTA (Spearman $\rho = -0.184$, $p = 0.008$).

Multivariate analysis using linear regression revealed that only the AC and BC thresholds retained a significant correlation with the difference in ABG before and after revision ($p < 0.001$). These data suggest that a greater pre-revision ABG may be correlated with a better Δ ABG (Tab. III).

Discussion

The present study investigated the outcomes and challenges of secondary stapedotomy procedures in a retrospective series of 308 cases, revealing that significant improvements in hearing are possible with prompt revision surgery. In our series, dislocation of the prosthesis or its shortness accounted for approximately 70% of surgical revisions (Cover figure). Previous studies also indicate that issues related to the stapedial prosthesis are the most common reason for revision surgery, albeit with a lower prevalence (up to 60%)^{10,12,20-22}.

In line with our data, displacement of the prosthesis was the most frequent cause^{10,21}. The high rate of prosthesis dislocation may be related to the type of prostheses used. Specifically, Teflon prostheses have been reported to have a dislocation rate of approximately 3% at 2 years after primary surgery²³. Also in our data set, Teflon prostheses showed a higher rate of dislocations compared to other prostheses (Tab. II). Although less frequent, the shortness of prosthesis used in primary surgery²¹ remains a common cause of revision. These problems are more susceptible to repair with a higher success rate than other issues described below¹⁰. Erosion of the incus long process is another prevalent reason for undergoing revision surgery, with occurrences reported between 5% and 32%^{9,10,21,22,24-26}. In our series, this event occurred in 17.2% of cases. The literature extensively debates the possible causes of incus erosion. The long process of the incus receives blood supply from the incudal artery, which originates from the ossicular branch of the anterior tympanic artery and supplies the mucosal arteries and the nutrient foramen within the incus body. The lenticular process also receives blood through anastomoses from the arteries of the stapes tendon and posterior crural artery²⁷. It was previously thought that avascular necrosis could occur

due to a compromised blood supply caused by an excessively tight crimping of the wire. However, Schuknecht refuted this, stating that the incus is well-supplied by a central nutrient vessel and a network of mucosal vessels sufficient to nourish the tip of the long process²⁷. More recent findings have indicated that the most part of nutrient foramina are in the upper two-thirds of the long process on its antero-medial side, a location generally unaffected by a crimped prosthesis²⁸. Nowadays, it is commonly accepted that incus necrosis is likely due to an overly loose crimp, allowing the prosthesis to continuously rub against and gradually wear down the long process²⁹. While this erosion is often associated with crimped wire, it can also occur with various other types of prostheses^{25,30}. The material of the prosthesis seems to favour a foreign body reaction. Platinum was suggested as a good option due to its malleability, but its use was associated with a higher occurrence of necrosis of the long process of the incus. Also in our data set, platinum-Teflon prostheses are associated with a higher rate of incus erosion than other prostheses. This increased rate of necrosis is believed to be associated with local toxicity or alterations in incus attachment^{29,31}. Data on rates of incus erosion and implant dislocation are not homogeneous in the literature (Tab. IV).

The variability in rates of incus erosion and prosthesis dislocation likely depends on the surgical technique used during the initial procedure and the type of prosthesis implemented. In our series, we observed a high percentage of prosthesis dislocations infrequently associated with incus erosion. The types of prostheses used in our series may explain the high rate of dislocation observed during revision surgery. Specifically, Teflon prostheses sometimes fail to adequately secure the long process of the incus, leading to dislocation without causing damage to the incus. Therefore, in our observations, a loosely crimped prosthesis that continuously moves does not gradually wear down the long process but

instead dislodges from it. Our data do not align with Sakano's claim that incus necrosis is due to a loose crimp that allows the prosthesis to continually rub and gradually erode the long process²⁹. Moreover, in our series, during the first surgical procedure, prostheses of different materials – Teflon, platinum-Teflon, titanium-Teflon, nitinol – were used, and prostheses in platinum-Teflon seemed to be associated with a higher prevalence of erosion of the incus.

Other causes of primary surgery failure, such as middle ear scarring, ankylosis, and perilymphatic fistula, were much less frequent. Adhesions and fibrous bands are occasionally observed. Some authors have reported that the incus and prosthesis may become immobilised due to dense fibrous tissue⁶, but the occurrence of adhesions is more common in stapedectomy compared to stapedotomy (20.6% vs 7.9%). This finding supports our data, as stapedotomy is considered a less invasive technique²¹. Schönfeld and collaborators emphasise the importance of avoiding damage to the mucosa around the oval window or promontory during initial surgery to prevent fibrosis that could adhere the prosthesis or incus to the promontory or tympanic membrane³⁴. In case of fibrous tissue and adherence, the use of a laser, particularly around the oval window, may facilitate a gentler removal of adhesions. One study highlighted that using an argon laser during revision surgeries increased successful outcomes from 70% to 91%, achieving an ABG within 10 dB. However, another more recent study found no significant impact on hearing improvement outcomes when comparing different energy levels of the laser or its use versus non-use in revision stapedectomy³⁴. In our series, scars around the piston and incus occurred in 6.4% of the surgical procedures, and we never used a laser to remove the fibrous bands.

To prevent persistent conductive hearing loss, it is critical to palpate the entire ossicular chain because a fixed malleus and/or incus may be congenital or caused by bone dust and

Table IV. Intraoperative findings in revision stapes surgery as reported in the literature.

References	Incus erosion	Displaced prosthesis	Short prosthesis
Bernardeschi et al. ³²	42.1%	20.6%	3.9%
Blijleven et al. ⁹	5%	27%	15%
Fernandez et al. ¹⁴	32%	26%	21%
Kanona et al. ³³	12%	8%	1%
Luryi et al. ⁸	38%	43%	-
Schwam et al. ²⁶	43.4%	24.5%	-
Lundman et al. ¹²	35.6%	48.2%	3.1%
Vincent et al. ¹¹	27.6%	18.2%	12.7%

Table V. Audiological outcomes after revision stapes surgery as reported in the literature.

Author	No. of cases	ABG ≤ 10 dB (%)	ABG ≤ 20 dB (%)	Dead ear (%)
Pedersen et al. ³⁵	163	51	75	1.2
Hammerschlag et al. ⁶	250	80	85	0
De La Cruz et al. ⁴⁰	356	60	78	1.4
Lippy et al. ²¹	483	71	86	0.002
Gros et al. ¹⁰	63	52.4	79.4	1.6
Schmid et al. ³⁶	172	55	84	1.2
Vincent et al. ¹¹	652	63	75	2.9
Bernardeschi et al. ³²	102	60	85	2
Fernandez et al. ¹⁴	34	68.5	89.5	0
Our data	308	57.2	76	0.3

fragments during primary surgery. This happened rarely (less than 4%) in our series, with 6 subjects affected (1.9% of cases) ^{6,12} and, unfortunately, there is no straightforward or uncomplicated way to resolve this problem. In 4 cases of our series, the surgeon performed a malleostapedotomy, cutting the head of the malleus with good but not optimal results.

Perilymphatic fistula is commonly encountered during revision surgeries performed due to the onset or persistence of vertigo. Typically, surgery is not indicated for sensorineural hearing loss following stapedectomy unless the patient experiences symptomatic vertigo suggestive of perilymphatic fistula. One study reported the incidence of delayed vertigo after stapedectomy as 0.5% ²². Another study indicated that perilymphatic fistula accounted for 9% of revision stapes surgeries, all associated with vertigo ²². This and other studies suggest that the presence of perilymphatic fistula is likely underestimated ²¹. Eight patients in our series had vertigo, and a perilymphatic fistula was found during surgical revision. The fistula was then sealed with perichondrium, leading to complete remission of symptoms. Literature data and our experience suggest that if a patient experiences vertigo (with or without sensorineural hearing loss), suspicion for perilymphatic fistula should be raised, and exploration should be performed.

The type of anaesthesia used for surgical revision is also important. Although any method of anaesthesia may be acceptable in primary surgery, local anaesthesia alone or local anaesthesia with sedation can have an advantage in revision surgery. If a patient suffers from dizziness while the surgeon manipulates or removes the previously placed prosthesis, this may indicate the presence of adhesions between the prosthesis and the sacculus. Without patient feedback, the surgeon may continue to manipulate or remove the pros-

thesis, placing the patient's hearing at risk. Nevertheless, we found a significant positive correlation between Δ ABG and general anaesthesia in univariate analysis ($p = 0.010$), although this was not confirmed in multivariate analysis.

The audiological results in our dataset are positive. ABG closure within 10 dB was achieved in 57.2% of cases and within 20 dB in 76%, with only one instance of profound sensorineural hearing loss. Revision surgery, however, remains challenging due to complications and its overall success rate, which is lower than that of primary surgery, even in the most experienced hands. Overall, ABG closure is 51-80% within 10 dB and 75-89.5% within 20 dB (Tab. V).

The risks of sensorineural hearing loss and vertigo are believed to increase with revision stapes surgery compared to primary stapes surgery. Historically, reported rates of sensorineural hearing loss after revision surgery have been as high as 20% ¹⁰. This increased risk may result from the distortion of normal anatomy due to prior surgery and unpredictable bony regrowth of the oval window. However, recent studies have shown a rate of sensorineural hearing loss of about 0-2.9% ¹¹. Recent scientific papers indicate low rates of cochlear damage. This could be attributed to the fact that these studies discuss revisions of stapedotomies, which appear to have a lower incidence of cochlear damage compared to revisions of stapedectomies ³⁷. Additionally, it is worth noting that very few authors have reported high rates of cochlear damage in the scientific literature ³⁸. These rates fall within the reported ranges for stapes surgery, suggesting that routine revision stapes surgery is safe in experienced hands.

Univariate analysis of individual factors showed that the mean preoperative ABG is a positive prognostic factor for successful surgery, and this finding was confirmed by multivariate analysis. Sharaf et al. consider the ABG a predictive

factor for success of revision stapedioplasty surgery³⁹. Additionally, previous stapedotomy was associated with higher success rates in revision surgery than previous partial or total stapedectomy²⁰.

Regarding intraoperative findings, prosthesis dislocation was associated with higher success rates than other primary causes of failure. Incus erosion and malleus-incus ankylosis were also associated with relatively high success rates²⁰. Moreover, the type of prosthesis placed during revision surgery was identified as a prognostic factor: a low rate of success was obtained for total ossicular prostheses compared with a high rate of success with other prostheses (pistons, wires, others)⁴⁰. Malleus-to-oval window interposition was associated with lower success rates than incus-to-oval window interposition⁴⁰.

Furthermore, the number of previous surgeries was identified as a negative prognostic factor⁴⁰. Considering all this data, the use of three variables – previous surgical technique, primary cause of failure, and type of prosthesis during revision surgery – can be used together in predicting success following stapes surgery²⁰. Differences in piston materials may confound comparisons of outcomes. Generally, it is acknowledged that there is no significant difference in hearing outcomes among the various types of pistons. Our study supports these findings. Approximately one-fourth of patients underwent revision stapedotomy using a laser. In our series, there were no significant differences between the laser and non-laser groups in terms of mean postoperative gap, the percentage of patients with a gap ≤ 10 dB, the mean change in sensorineural hearing loss, or the percentage of cases with improved hearing. Similar results have been described by other authors⁴⁰.

Surgical success can also be enhanced by understanding the cause necessitating revision surgery beforehand. Additionally, because some primary surgical procedures are performed at other institutions, information on primary surgical techniques and prostheses may be limited. In such cases, CT can be helpful. In our case series, CT identified the problem in more than half of cases. However, it is important to note that CT can miss imperceptible findings such as prosthesis displacement, incus erosion, or dehiscence of the superior semicircular canal. Therefore, the images should be reviewed collaboratively by radiologists and surgeons who are experienced in stapes surgery.

Conclusions

Revision stapedoplasty is feasible and yields good results with a low risk of cochlear damage. In our series, the pri-

mary intervention was always a stapedotomy. Therefore, future revisions will be predominantly revisions of stapedotomies. Intraoperatively, prosthesis dislocation was the most frequent finding, while incus erosion was infrequent. This can be attributed to the good performance of modern prostheses. The combination of primary stapedotomy and prosthesis dislocation leads to excellent surgical outcomes with an almost zero rate of cochlear damage.

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

LB: conceptualization, writing – original draft preparation, writing – review and editing; LB, FL: methodology; FL: software; FF, LB, SB: validation; FL, LB: formal analysis; OM: investigation; all the authors: data curation, visualization; DC, AA, EC, AC: supervision; SB: project administration. All authors have read and agreed to the published version of the manuscript.

Ethical consideration

This study was approved by the Institutional Ethics Committee. Local Review Board do not release acceptance codes for retrospective studies based on clinical practice measures. The research was conducted ethically, with all study procedures being performed in accordance with the requirements of the World Medical Association's Declaration of Helsinki.

Written informed consent was obtained from each participant/patient for study participation and data publication.

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