INDONESIAN HEALTH JOURNAL
https://ihj.rivierapublishing.id/index.php/rp
Volume 4 Number 4, December 2025
P-ISSN: 2963-3044
E-ISSN: 2963-3036

A New Strategy for Presbycusis: A Literature Review on Stem Cell Therapy for Hair Cell and Auditory Neuron Regeneration

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Abstract

Presbycusis, or age-related hearing loss, is the leading cause of hearing loss among the elderly, leading to decreased quality of life and mental health issues. While existing treatments offer some benefits, they have limitations and do not address the degenerative nature of presbycusis. This literature review examines the regenerative potential of stem cell therapy and its derivatives for cochlear hair cells and auditory neurons in cases of presbycusis. A search was conducted across PubMed, ScienceDirect, and Google Scholar to identify literature published from 2020 to 2025 that studied stem cells and their derivatives for hair cell and auditory neuron regeneration in presbycusis models. Three preclinical studies using bone marrow-derived mesenchymal stem cells (MSCs) in rodent models demonstrated the regeneration of hair cells and auditory neurons, with evidence of hearing improvement. Each study employed unique MSC modifications using advanced techniques, such as gene editing and extracellular vesicle derivation, to enhance anti-inflammatory and antiapoptotic properties. Stem cell-based therapies for presbycusis show promise but remain in early developmental stages. Major challenges include optimizing delivery methods (intracochlear, intratympanic, or intravenous routes), ensuring long-term safety profiles, preventing immune rejection and tumorigenicity, establishing standardized protocols for cell preparation and dosing, and addressing high treatment costs. Further clinical and local research is essential to facilitate the implementation of this therapy in Indonesia.

Keywords: auditory neurons, hair cells, presbycusis, regeneration, stem cells

INTRODUCTION

Presbycusis, or age-related hearing loss (ARHL), is a bilaterally progressive, irreversible sensorineural hearing loss (SNHL) that predominantly occurs in the population over 65 years old (Yang et al., 2023; Labambe et al., 2023; Wang & Puel, 2020). According to the World Health Organization (WHO), presbycusis affects more than 65% of adults over 60 years old, making it the most common cause of hearing loss in the older population. As the elderly population grows, it is estimated that by 2025, over 500 million seniors will experience presbycusis globally (Labambe et al., 2023). In 2023, the Central Statistics Bureau of Indonesia stated that there were 29.3 million adults over 60 years old in Indonesia (Badan Pusat Statistik, 2024). Hearing loss affects 36.6% of the population above 75 years old and 17.1% of the population between 65 and 74 years old in Indonesia, according to the National Health Research in 2021 (Kementerian Kesehatan Republik Indonesia, 2013).

Aging and many other factors cause changes in the inner ear. The most common changes are atrophy of the stria vascularis and loss of fibrocytes of the spiral ligament in the lateral wall of the cochlea (strial or metabolic type presbycusis), decrease of sensory hair cells (sensory type presbycusis), and degeneration of the auditory nerve (neural type presbycusis). These changes result in high-frequency hearing loss that may progress to low-frequency hearing loss, reduced understanding of speech in noisy environments, slowed central processing of acoustic information, and impaired localization of sound sources. Elderly people with presbycusis are reported to experience communication difficulties, reduced quality of life, social isolation, cognitive decline, depression, dementia, and Alzheimer's disease (Yang et al., 2023).

Until today, the primary treatments for presbycusis have been hearing aids and cochlear implants. Although these devices improve communication and quality of life, they often provide unnatural sound perception and are less effective in noisy environments. Additionally, some people are reluctant to wear hearing aids and cochlear implants due to stigmatization in the community and the difficulty in using the devices (Labambe et al., 2023; Saraswati et al., 2024; Zhang et al., 2022). Moreover, neither hearing aids nor cochlear implants can repair damaged auditory nerves or inner ear structures, making them unable to restore natural hearing fully (Lin et al., 2025).

The limited regenerative capacity of human hair cells and auditory neurons has been an obstacle in presbycusis therapy for decades (Lin et al., 2025). However, medical research in recent years has advanced toward regenerative medicine. These studies offer hope for a new therapy for presbycusis, which was once considered irreversible. In the last decades, we have seen promising results from in vitro and animal studies showing that stem cells from various sources can be developed into hair cells and auditory neurons in the cochlea with SNHL (Hussain et al., 2017; Chorath et al., 2020; Kanzaki et al., 2020).

Despite the growing body of research on stem cell therapy for various types of sensorineural hearing loss, there exists a significant gap in the literature specifically addressing presbycusis. Most existing studies focus on acute hearing loss models, noise-induced hearing loss, or ototoxic damage, while the complex, multifactorial pathophysiology of age-related hearing loss has received less attention. Furthermore, previous systematic reviews have examined stem cell therapy for SNHL in general but have not comprehensively analyzed the specific challenges and opportunities presented by presbycusis as a distinct clinical entity. This literature review addresses these gaps by specifically examining stem cell-based interventions for age-related hearing loss, analyzing the unique mechanisms involved in aging-related cochlear degeneration, and evaluating the translational potential of these therapies in the context of presbycusis management.

This review critically evaluates the latest research on stem cell-based therapy for presbycusis, examining their regenerative impact on cochlear hair cells and auditory neurons, therapeutic outcomes, development prospects, and clinical implementation challenges. The specific objectives are to: (1) identify and analyze current preclinical evidence for stem cell therapy in presbycusis models, (2) evaluate the mechanisms by which different stem cell modifications enhance therapeutic efficacy, (3) compare delivery methods and their effectiveness in reaching cochlear targets, and (4) discuss the translational challenges and future directions for clinical implementation, particularly in the Indonesian healthcare context.

METHOD

In this literature review, a comprehensive literature search was conducted between April and May 2025 across electronic databases, namely: Google Scholar, PubMed, and ScienceDirect. The search terms and Boolean operators used were: ("presbycusis" OR "age-related hearing loss") AND ("stem cell" OR "regeneration") AND ("hair cells" OR "auditory neuron").

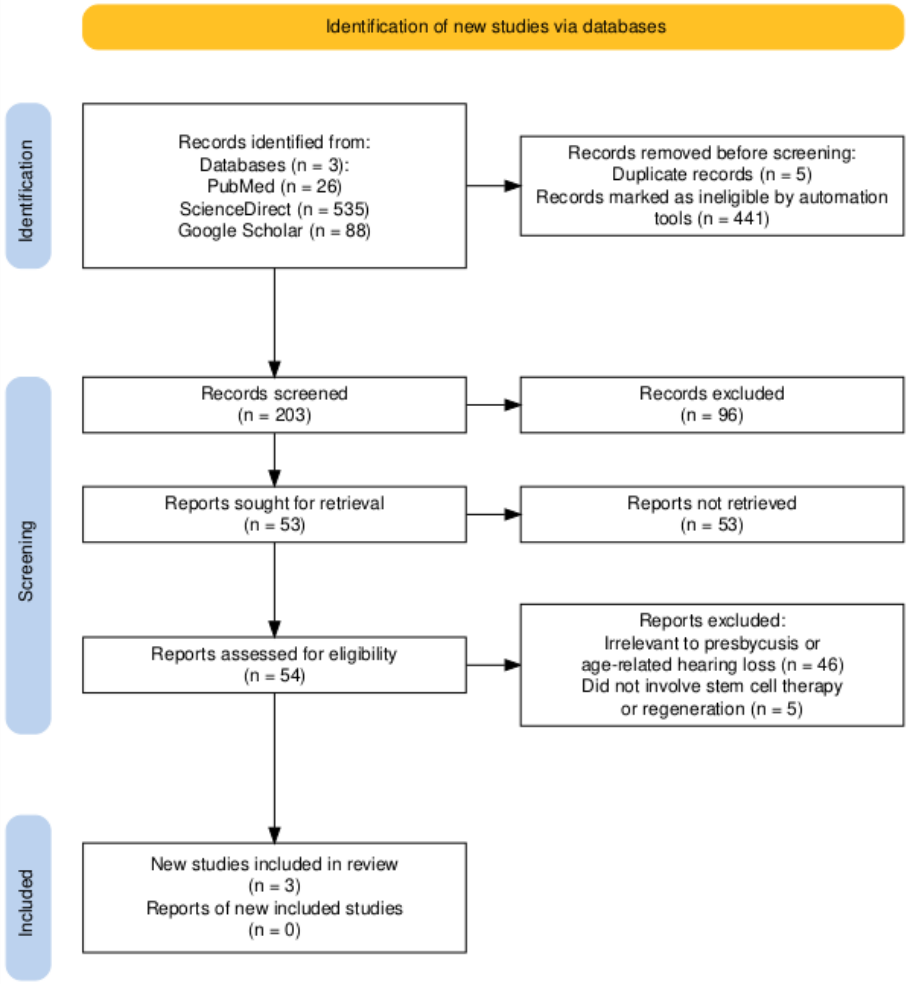

Figure 1. PRISMA flow diagram

The inclusion criteria for this research are: (1) peer-reviewed original research articles, including in vitro, in vivo, and clinical trials; (2) articles published between January 2020 and May 2025 to ensure current and relevant findings; (3) studies focusing specifically on the application of stem cells and their derivatives in the treatment of presbycusis or age-related hearing loss models; and (4) studies that clearly reported outcomes related to hair cell regeneration, auditory neuron survival, or hearing function improvement. The exclusion criteria are: (1) review articles, editorials, commentaries, and conference abstracts, as these do not provide original empirical data; (2) unavailable full texts; (3) studies that do not specifically address presbycusis or age-related hearing loss, including those examining acute hearing loss, noise-induced hearing loss, or drug-induced ototoxicity without age-related components; and (4) articles not available in English, due to translation limitations and to ensure accurate interpretation of methodology and findings.

Quality assessment of included studies was conducted using standardized criteria adapted from the SYRCLE's risk of bias tool for animal studies. Each study was evaluated for: (1) adequate randomization and allocation concealment, (2) blinding of investigators and outcome assessors, (3) completeness of outcome data, (4) selective outcome reporting, and (5) other sources of bias including sample size justification and appropriate statistical methods. Studies were categorized as having low, unclear, or high risk of bias for each domain.

A standardized data extraction form was developed to collect pertinent information from each included study, namely: study details (authors, year of publication), study design, stem cell type/origin, intervention details, and key findings. A PRISMA flow diagram is provided in Figure 1. Two independent reviewers conducted the initial screening of titles and abstracts, followed by full-text assessment of potentially eligible studies. Any disagreements were resolved through discussion and consensus.

RESULTS AND DISCUSSION

Keyword search on Google Scholar yielded 88 articles, while PubMed yielded 26 articles, and ScienceDirect yielded 535 articles. Among those, duplicate articles (n=5), publications before the year 2020 (n=441), review papers and other non-original research papers (n=96), and articles with no full text available (n=53) were excluded. Among the 54 articles thoroughly assessed, articles that were irrelevant to presbycusis or age-related hearing loss (n = 46) and did not involve stem cells or regeneration therapy (n = 5) were excluded. Reference lists of selected studies were also screened but yielded no additional relevant articles. Ultimately, we identified only three original research articles that investigated stem cells in presbycusis.

All three studies utilized bone marrow-derived mesenchymal stem cells (MSCs) to promote the regeneration of hair cells or auditory neurons in animal models of presbycusis. They were all pre-clinical studies, combinations of *in vitro* studies followed by *in vivo* studies, conducted in China, and were published between 2024 and 2025. Two studies used H_2O_2-induced HEI-OC1 (House Ear Institute-Organ of Corti 1) cells, and one study used ouabain-damaged cultured spiral ganglion neurons (SGNs) for the *in vitro* study. HEI-OC1 is a mouse inner ear cell line derived from the organ of Corti, commonly used in hearing research. Two studies used Sprague-Dawley rats. One study induced the rats with D-galactose to model ARHL rats with damaged outer hair cells (OHCs), while another induced the rats with ouabain to model degenerated SGNs in ARHL rats. While the other study used aged (18–19 months old) CBA/CaJ mice as the ARHL animal model.

All three studies used bone marrow-derived MSCs, but each employed unique MSC modifications using advanced techniques. Liu *et al.* utilized lentiviral as vector to introduce the

growth differentiation factor (GDF)15-overexpressing gene into MSCs. The increase of GD15 upregulated sirtuin 1 (SIRT1) protein expression and, in turn, amplified the MSC regeneration effect on OHCs.(12) Xu *et al.* used lentiviral transduction to create MSCs overexpressing Apelin and combined these cells with their derived extracellular vesicles (EVs) to enhance therapeutic efficacy. The treatment suppressed inflammation and promoted hair cell survival by supporting anti-inflammatory processes.(13) Meanwhile, Chen *et al.* focused on observing the effect of the small EV (sEV) produced by MSCs (MSC-sEV). In their study, they delivered the MSC-sEV via intratympanic injections instead of intracochlear injections via the round window, like the other two studies.(14)

All three studies used different staining and tests to assess the MSC effect *in vitro* and *in vivo*. They all used hearing tests such as auditory brainstem response (ABR) and distortion product otoacoustic emissions (DPOAE) to assess MSCs' effect on hearing *in vivo*. The design, interventions, and outcomes of the three included studies were summarized in **Table 1**.

Table 1. Studies of stem cell impact on hair cells and auditory nerve in presbycusis

Study Design	Presbycusis Model	Stem cell type	Intervention	Key findings	References
In vitro *In vivo*	H_2O_2-induced HEI-OC1 cells D-galactose-induced SD rat	Bone marrow-derived MSCs	MSCs-NC/ MSCs-GDF6 (1 × 10^5 cells/ mL) retro-auricularly injected into the scala media or tympani of the cochlea	• In H2O2-induced HEI-OC1 cells, GDF15 and SIRT1 was significantly decreased, inducing apoptosis • GDF15 overexpression decreased the LC3 II/LC3 I ratio and number of LC3-positive autophagosomes, restoring autophagic flux • In a rat model, MSC treatment increased GDF15 and SIRT1 expression • Reduced ABR thresholds • Recovered and decreased the loss of OHCs • Downregulated autophagy-related proteins (LC3 II/LC3 I, p62) and pro-apoptotic-related proteins (Bax and cleaved caspase-3) • Upregulated the Bcl-2 anti-apoptotic-related protein	Liu *et al*, 2025(12)
In vitro *In vivo*	H_2O_2-induced HEI-OC1 cells 18-19 months old CBA/CaJ male mice	Bone marrow-derived MSCs and the EVs	MSCs (1 × 10^7 cells/ mL) injected into the cochlea via the round window membrane EVs.sh-NC or EVs.sh-Apelin (60 μg/mL) injected	• In the EVs.oe-Apelin + HEI-OC1 group, there was noticeably less aging, accompanied by downregulation of the aging-related proteins P53 and P21, increased cell vitality, and decreased cell apoptotic rate • In a rat model, MSCs were able to differentiate into inner ear auditory cells • Significant decrease in ABR and DPOAE hearing thresholds in the second and fourth weeks post MSC transplantation • Significant upregulation of Cx26 and Na–K ATP expression in the cochlear tissue • Upregulated Apelin expression, resulting in reduced pro-inflammatory M1 macrophages percentage, downregulation of IL-6 and IL-1β expression, and increase anti-inflammatory M2 macrophages percentage, upregulation of IL-10 and Arg1 expression	Xu *et al*, 2025(13)

			into the tail vein for 4 weeks	• Effects were most enhanced in the EVs.oe-Apelin group	
In vitro *In vivo*	ouabain-damaged cultured SGNs ouabain-induced SD rat	sEV from bone marrow-derived MSCs	MSC-sEV (200 μg/ml) injected into the tympanic cavity	• In cultured SGNs, MSC-sEV promoted significantly longer neurites and axons than the control group • Reverse the degenerative effect of ouabain on cultured SGNs • Strongly promote growth cones with more spread and better-developed filopodia, even after ouabain damage • In a rat model, MSC-sEV rescued the decreased amplitude, prolonged latency, and threshold shifts in ABR induced by ouabain, restoring hearing function to normal • Reinstate SGNs density, inhibiting apoptosis after damage by ouabain	Chen *et al*, 2024(14)

ABR: auditory brainstem response; ARHL: age-related hearing loss; ATP: adenosine triphosphate; Bcl-2: B-cell lymphoma 2; DPOAE: distortion product otoacoustic emissions; EVs.sh-Apelin: extracellular vesicles form MSCs with knockdown of Apelin; EVs.sh-Apelin: extracellular vesicles form MSCs with overexpression of Apelin; GDF: Growth differentiation factor; HEI-OC1: House Ear Institute-Organ of Corti 1; IL: interleukin; LC3: light chain 3; MSCs: mesenchymal stem cells; MSCs-GDF6: GDF6 overexpression-induced MSCs; MSC-sEV: Mesenchymal stem cell-derived small extracellular vesicles; NC: negative control; OHCs: outer hair cells; SD: Sprague Dawley; sEV: small extracellular vesicles; SGNs: spiral ganglion neurons; SIRT1: sirtuin 1.

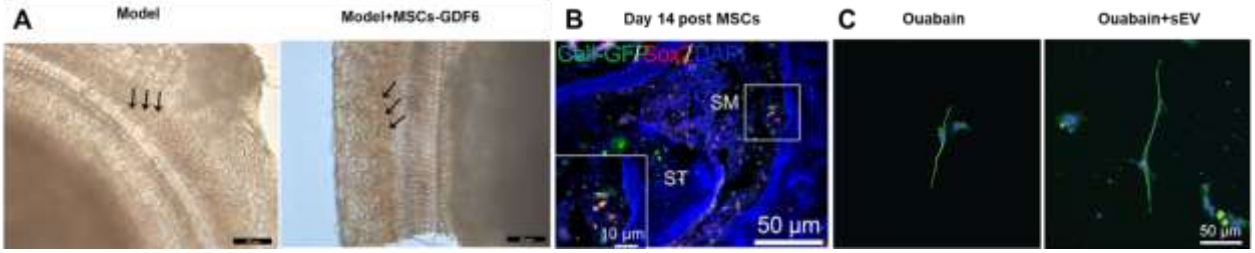

Figure 2. MSCs regenerating hair cells and SGNs. A. Silver nitrate staining showing three rows of outer hair cells (arrows) in the cochlea. Scale bar: 50 μm.(12) **B.** Immunofluorescence (IF) staining of cochlear vestibule and middle ear showing MSC-GFP (green), Sox2 (red), and DAPI (blue).(13) **C.** IF staining of SGNs showing the length of neurites. Scale bar: 50 μm.(14)

Beyond the neonatal period, the mature sensorineural tissues of the mammalian cochlea, including hair cells and SGNs, lose their innate ability to regenerate, rendering most SNHL irreversible (Zhang et al., 2022; Rzepakowska et al., 2024). This has led to growing interest in stem cells and derivative therapies as emerging solutions for presbycusis. Stem cells have the capacity for self-renewal and pluripotency, meaning they can continuously divide and differentiate into all types of cells depending on the stimuli. Their potential for cell regeneration, repair, and replacement makes stem cell therapy very auspicious. Based on their origin and potency, stem cells are classified into several types. The first one to ever be studied is embryonic stem cells (ESCs), which originate from a 5-day-old pre-implantation blastocyst and are pluripotent. Adult stem cells (ASCs) are multipotent cells that originate from various tissues in the body. One of their subtypes is MSCs. Induced pluripotent stem cells (iPSCs) are well-differentiated cells that are genetically reprogrammed into pluripotent cells (Nourbakhsh et al., 2021).

Stem cells regenerating hair cells and SGNs

All three studies in this review have shown promising outcomes of stem cell therapy, particularly MSCs, for presbycusis. MSCs are a type of ASCs that originate from mesodermal cells present in the umbilical cord, muscle, adipose, and bone marrow. Previous studies have shown their ability to differentiate into various tissues, including hair cells and auditory neurons (Chorath et al., 2020; Kanzaki et al., 2020).

Histological findings across the three studies support the regenerative effects of MSCs on OHCs and SGNs. Liu et al. demonstrated that MSC therapy restored the orderly arrangement of OHCs and mitigated their loss in ARHL rats, as evidenced by cochlear silver nitrate staining (Figure 2A) (Liu et al., 2025). Xu et al., employing fluorescent labeling of green fluorescent protein (GFP), Myo7a, and Sox2 to identify MSCs, inner ear hair cells, and auditory progenitor cells, respectively, observed that migratory MSCs were present in the scala vestibuli, scala media, and scala tympani, where they differentiated into GFP+Sox2+Myo7a+ cells which were hair cell progenitor (Figure 2B). By day 28, MSCs were also detected in the apex of the organ of Corti, further differentiating into Myo7a+, Sox2+, and Sox2+Myo7a+ cells, as confirmed by immunofluorescence labeling (Xu et al., 2025).

Chen et al. reported that, in vitro, SGNs treated with MSC-sEV exhibited significantly longer neurite and axon lengths compared to controls and the ouabain group (Figure 2C), with results comparable to those achieved with high concentrations of brain-derived neurotrophic factor (BDNF), likely due to the synergistic effects of BDNF and other neurotrophic factors contained within MSC-sEV. No differences were observed in axon number across groups,

potentially attributable to the pseudounipolar nature of SGNs, which limits their capacity for new axon formation despite their ability to extend new neurites in vitro (Chen et al., 2024). These findings support existing evidence from previous studies showing that MSCs can migrate to and differentiate within the cochlea, indicating their potential to restore hearing and stimulate hair cell regeneration following transplantation (Zhang et al., 2022; Chorath et al., 2020).

Stem cells improve hearing test results

The efficacy of MSC treatment is indicated by the improvement of hearing tests in the MSCs group compared to the negative control group. In the study by Liu et al., the ABR threshold at 8, 12, and 24 kHz was decreased by > 20 dB SPL ($p < 0.01$) in the MSCs group compared to the negative control group. This effect was even more pronounced in the MSCs-GDF6 group, where an ABR threshold decrease of > 40 dB SPL ($p < 0.01$) was observed compared to the negative control group (Liu et al., 2025). Xu et al. found a similar result, in which a significant decrease in ABR and DPOAE threshold was observed in the MSCs group compared to the negative control, especially at 8, 12, and 16 kHz. However, the effect only appeared after the second and fourth weeks of MSC treatment (Xu et al., 2025). A similar finding was reported in a 2020 systematic review by Chorath et al., which examined the effects of MSCs on SNHL. The review found that the most significant therapeutic effects were observed when > 10^7 cells were administered (−26.70; 95% CI: [−35.91, −17.50]), delivered to extracochlear (−25.51; 95% CI: [−29.51, −21.50]) and occurred within 1–2 weeks following the onset of SNHL (−23.23; 95% CI: [−26.75, −19.72]). Additionally, repeated administrations were associated with further improvements in auditory brainstem response (ABR) (−25.23; 95% CI: [−29.68, −20.78]) (Chorath et al., 2020). These findings can help guide the dose and course of MSC therapy in the future. Furthermore, when applied to children with acquired SNHL, Baumgartner et al. reported enhanced language development accompanied by improved white matter myelination on magnetic resonance imaging (MRI) following MSC therapy (Baumgartner et al., 2018).

Xu et al. also found marked upregulation of Cx26 and Na–K ATP expression in immunofluorescent staining of the cochlear tissue after MSC transplantation (Xu et al., 2025). Na–K ATPase in the stria vascularis and the spiral ligament is essential to maintain high potassium concentration in the endolymph and therefore positive endocochlear potential of +80 to +100 mV. The Cx26 protein enables the movement of ions and small molecules between neighboring cells by forming channels that link them together. Cx26 and Na–K ATP have a major role in preserving physiologic depolarization caused by hair cells and the following neurotransmitter release into the synaptic cleft of the hair cells and auditory neurons (Yang et al., 2023; Xu et al., 2025).

Meanwhile, in the study by Chen et al., ouabain injection specifically induced SGNs degeneration and did not damage OHCs. Therefore, the DPOAEs and ABR interwave I-IV latencies remain unaffected. This aligns with the theory that DPOAE measures the health of the outer hair cells and overall cochlear function. Lower DPOAE levels suggest poorer hearing. ABR measures the electrical signals travelling from the ear to the brain. Higher ABR thresholds indicate worse hearing ability. Nonetheless, the ouabain group exhibited a noticeable decrease in amplitude, delay in latency, and a dramatic increase in ABR wave I thresholds across high frequencies, particularly at 32 kHz, with approximately a mean 35 dB shift. This disruptive effect of ouabain was not observed in the ouabain+MSC-sEV group, as the hearing function parameters in this group were close to the positive control group. This finding suggested that

MSC-sEV can restore hearing function to nearly normal levels, even after SGNs degeneration has occurred (Chen et al., 2024).

A systematic review by Zhang et al. evaluated the effect of various stem cells in animal models for SGNs regeneration in SNHL. Among the 28 studies reviewed, only 11 studies mentioned ABR outcomes after MSC treatment. Among these, 7 studies demonstrated varying degrees of improvement in ABR thresholds, while no improvement was noted in the other 4 studies. A meta-analysis of four selected studies demonstrated that MSCs enhanced overall hearing performance, with a combined effect size indicating +9.10 dB enhancement in DPOAE measurements and a −15.22 dB reduction in ABR thresholds, corroborating other findings of better cochlear and neural auditory function after MSC treatment (Zhang et al., 2022).

Exploration of stem cell-derived therapy

Each study in this review explored the use of MSCs differently, showing the vast possibilities of MSC development. Despite the different biological and technical approaches, they all targeted cellular stress, inflammation, and apoptosis as the key mechanisms underlying degeneration in presbycusis. In their study, Liu et al. utilized lentiviral as vector to integrate the GDF15-overexpressing gene into one of the MSC lines. GDF15 is a growth factor that is in charge of responses to inflammatory stimuli, oxidative stress, and apoptosis regulation. They work by downregulating autophagy-related proteins (LC3 II/LC3 I, p62) and pro-apoptotic-related proteins (Bax and cleaved caspase-3) and restoring autophagic flux. Functional autophagic flux is essential for cells to cope with stress by removing damaged mitochondria (mitophagy), reducing ROS, recycling components for survival, and in turn suppressing apoptosis. GDF15 also positively regulated SIRT1 protein expression, which is a class III histone deacetylase that has anti-aging, anti-inflammatory, and antioxidant effects. Targeting this GDF15/SIRT1 pathway, Liu et al. successfully amplified the MSC regeneration effect on OHCs (Liu et al., 2025).

A study by Xu et al. also employed lentiviral transduction to establish Apelin-overexpressing MSC lines. Apelin is one of the peptides contained in the EVs involved in regulating inflammation and vascular functions by reducing pro-inflammatory M1 macrophage percentage and IL-6 and IL-1β expression while increasing anti-inflammatory M2 macrophage percentage, and IL-10 and Arg1 expression. This results in the suppression of inflammation and promotion of the anti-inflammation process, salvaging the hair cell vitality (Xu et al., 2025).

Consistent with these findings, Chorath et al. demonstrated that MSCs can influence immune responses by promoting IL–10–producing regulatory T cells, which suppress Th1 and Th17 pro-inflammatory pathways, further reinforcing their anti-inflammatory potential (Chorath et al., 2020).

One of the concerns regarding regenerative therapy is about safety. Previous research has demonstrated that MSC therapy for other diseases is generally well-tolerated compared to other types of stem cells, with no signs of toxicity affecting the lungs, blood, kidneys, or nervous system. MSCs possess immunomodulatory properties that support successful transplantation and minimize the likelihood of immune rejection. Additionally, MSCs are more efficient, practical, and associated with a lower risk of tumor development (Chorath et al., 2020; Kanzaki et al., 2020; Tavanai et al., 2024). However, EVs, as seen in studies by Xu et al. and Chen et al., have emerged as an alternative to MSCs in the latest research. EVs are small lipid-bound vesicles released by cells, containing proteins, RNAs, and lipids, that are crucial in cell signaling between macrophages and various other immune cells. They mainly influence the polarization of macrophages into M1 or M2, which in turn affects inflammation and tissue regeneration (Hu et al., 2021). They gained interest due to their low immunogenicity, tumorigenic risk, and

enhanced safety profile compared to MSCs, as well as ease of storage and transport owing to their acellular nature (Chen et al., 2024; Hu et al., 2021).

Delivering stem cells or EVs precisely into the inner ear remains another technical challenge due to the cochlea's delicate and enclosed anatomy. In general, intravenous delivery of MSCs has been confirmed as safe in human studies; however, it has shown limited effectiveness in improving hearing outcomes in SNHL (Kanzaki et al., 2020). EVs are smaller than MSCs (± 30–150 nm), making them less prone to being trapped in the lungs during initial circulation, avoiding the pulmonary first-pass effect. This property also enables EVs to cross the blood-labyrinth barrier and reach the inner ear. Here's where EVs offer advantages compared to MSCs when commonly delivered via intravenous injection (Chen et al., 2024; Hu et al., 2021). However, it requires a higher dosage, which carries the risk of particle aggregation and micro-embolism. Additionally, the injected material may be quickly eliminated from the bloodstream by the mononuclear phagocyte system, leading to a shorter half-life and diminished therapeutic effectiveness (Chorath et al., 2020; Kanzaki et al., 2020; Chen et al., 2024). Another common MSCs and EVs delivery route is intracochlear injection. A new approach via intratympanic injection answers concerns about injury risk to the inner ear with the cochlear injection (Chorath et al., 2020; Kanzaki et al., 2020). Meanwhile, for targeted delivery of MSCs or EVs to the SGN, Li et al. developed a novel, minimally invasive surgical route to directly access the cochlear nerve via the round window (RW) and modiolus, reaching the fundus of the internal auditory meatus (IAM). Using synchrotron phase-contrast imaging (SR-PCI) and 3D modeling, the team mapped a safe drilling path that preserves critical vascular and vestibulocochlear structures (Li et al., 2024; Li et al., 2022).

Warnecke et al. conducted the first-in-human study of intracochlear administration of EVs derived from umbilical cord MSCs. These clinical-grade EVs were prepared under good manufacturing practice conditions and injected into the cochlea of a patient with Menière's disease during cochlear implantation. The procedure was well-tolerated with no adverse effects over 24 months and preserved cochlear function. Notably, the patient showed improved speech perception in noise, supporting the safety, feasibility, and potential therapeutic benefit of EV-based treatments (Warnecke et al., 2021).

Challenges for stem cell therapy

Despite promising results in preclinical studies, the clinical application of stem cells and derivative therapy for presbycusis faces numerous challenges. Particularly with embryonic or genetically modified stem cells, safety concerns, including the risk of immune reactions, inflammation, off-target effects of vectors, uncontrolled cell proliferation, and potential tumor formation, remain significant barriers. Moreover, regenerated cells often exhibit immature phenotypes, limiting their ability to functionally integrate into cochlear structures. The question of which cell sources, what stage of MSC differentiation, and what dose would be most suitable for engraftment remains unresolved, as does the process of neural network reorganization following transplantation and long-term efficacy. Moreover, the lack of standardized protocols, various cell sources, limited number of clinical trials contribute to the slow translation of these therapies into clinical practice. The high cost of research and clinical implementation, as well as ethical concerns, and unclear regulation of this therapy, also became a challenge, especially in Indonesia (Kanzaki et al., 2020; Xu et al., 2025; Rzepakowska et al., 2024; Tavanai et al., 2024).

Study Limitations

There are several limitations in this review. First, we only found 3 relevant preclinical articles, and none of them were clinical research on presbycusis. Most of the articles we found discussed stem cells and gene therapy for SNHL in general. Second, the studies were all conducted in China, which may limit the generalizability of the findings due to differences in research practices, regulatory frameworks, and clinical contexts across regions. Third, these studies lack reports on long-term outcomes and safety profiles, immune response risk, potential tumorigenicity, and variability in MSC preparations.

CONCLUSION

Presbycusis, or age-related hearing loss, is a progressive and irreversible condition primarily caused by the degeneration of cochlear hair cells and auditory neurons. Recent preclinical studies have shown that stem cell-based regenerative therapies hold promising potential to restore these damaged structures and improve hearing function. Evidence from in vitro and in vivo models demonstrates the ability of MSCs and their EVs to promote hair cell regeneration, enhance auditory neuron survival, and improve hearing function. However, despite these encouraging results, several challenges remain—particularly in optimizing delivery methods, ensuring long-term safety, managing potential immune responses, reducing cost, and addressing ethical and legal issues. Further research, especially in human trials and locally adapted studies in Indonesia, is essential to validate and adapt these therapies into clinical practice.

REFERENCE

Badan Pusat Statistik. (2024). *Statistik Penduduk Lanjut Usia 2024*. Badan Pusat Statistik.

Baumgartner, L. S., Moore, E., Shook, D., Messina, S., Day, M. C., Green, J., Cox, C., & Staecker, H. (2018). Safety of autologous umbilical cord blood therapy for acquired sensorineural hearing loss in children. *Journal of Audiology & Otology, 22*(4), 209–222.

Chen, A., Qu, J., You, Y., Pan, J., Scheper, V., Lin, Y., Jiang, W., Shi, F., & Yang, S. (2024). Intratympanic injection of MSC-derived small extracellular vesicles protects spiral ganglion neurons from degeneration. *Biomedicine & Pharmacotherapy, 179*, Article 117329.

Chorath, K., Willis, M., Morton-Gonzaba, N., & Moreira, A. (2020). Mesenchymal stem cells for sensorineural hearing loss: A systematic review of preclinical studies. *Molecular Biology Reports, 47*, 4723–4736.

Hu, Q., Lyon, C. J., Fletcher, J. K., Tang, W., Wan, M., & Hu, T. Y. (2021). Extracellular vesicle activities regulating macrophage- and tissue-mediated injury and repair responses. *Acta Pharmaceutica Sinica B, 11*, 1493–1512.

Hussain, B., Ali, M., Qasim, M., Masoud, M. S., & Khan, L. (2017). Hearing impairments, presbycusis and the possible therapeutic interventions. *Biomedical Research and Therapy, 4*(4), 1228–1247.

Kanzaki, S., Toyoda, M., Umezawa, A., & Ogawa, K. (2020). Application of mesenchymal stem cell therapy and inner ear regeneration for hearing loss: A review. *International Journal of Molecular Sciences, 21*, 1–15.

Kementerian Kesehatan Republik Indonesia. (2013). *Riset Kesehatan Dasar 2013* (pp. 283–286). Badan Penelitian dan Pengembangan Kesehatan.

Labambe, N., Sanna, A. T., Maulani, D., Sulaiman, A. B., & Hamriani, I. (2023). Characteristics of presbycusis: A literature review. *Journal of Eduhealth, 15*(3), 2024.

Li, H., Agrawal, S., Rohani, S. A., Zhu, N., Cacciabue, D. I., Rivolta, M. N., Bance, M., & Hartley, D. E. H. (2022). Unlocking the human inner ear for therapeutic intervention. *Scientific Reports, 12*(1), Article 4847.

Li, H., Agrawal, S., Zhu, N., Cacciabue, D. I., Rivolta, M. N., Hartley, D. E. H., & Bance, M. (2024). A novel therapeutic pathway to the human cochlear nerve. *Scientific Reports, 14*(1), Article 26795.

Lin, X., Xu, Y., Fan, C., & Zhang, G. (2025). Novel insights into mechanisms and therapeutics for presbycusis. *Heliyon, 11*, Article e41174.

Liu, J., Peng, H., Liu, Y., Li, C., & Xie, W. (2025). Therapeutic effects of GDF6-overexpressing mesenchymal stem cells through upregulation of the GDF15/SIRT1 axis in age-related hearing loss. *Frontiers in Bioscience (Landmark Edition), 30*(1), Article 2.

Nourbakhsh, A., Colbert, B. M., Nisenbaum, E., El-Amraoui, A., Dykxhoorn, D. M., Koehler, K. R., & Hashino, E. (2021). Stem cells and gene therapy in progressive hearing loss: the state of the art. *Journal of the Association for Research in Otolaryngology, 22*, 95–105.

Rzepakowska, A., Borowy, A., Siedlecki, E., Wolszczak, M., & Radomska, K. (2024). Contemporary directions in the therapy of sensory hearing loss. *Otolaryngologia Polska, 78*(4), 29–38.

Saraswati, I. A., Suprayogi, B., Utomo, R., & Trixie, A. (2024). Correlation of hearing aid use and quality of life in elderlies: A systematic review. *ORLI, 54*(2), 156–164.

Tavanai, E., Rahimi, V., Khalili, M. E., Falahzadeh, S., Zarandy, M. M., & Mohammadkhani, G. (2024). Age-related hearing loss: An updated and comprehensive review of the interventions. *Iranian Journal of Basic Medical Sciences, 27*, 256–269.

Wang, J., & Puel, J. L. (2020). Presbycusis: An update on cochlear mechanisms and therapies. *Journal of Clinical Medicine, 9*(1), Article 218.

Warnecke, A., Prenzler, N., Harre, J., Köhl, U., Gärtner, L., Lenarz, T., & Laner, A. (2021). First-in-human intracochlear application of human stromal cell-derived extracellular vesicles. *Journal of Extracellular Vesicles, 10*(7), Article e12094.

Xu, S., Liu, D., Zhang, F., & Tian, Y. (2025). Innovative treatment of age-related hearing loss using MSCs and EVs with Apelin. *Cell Biology and Toxicology, 41*(1), Article 31.

Yang, W., Zhao, X., Chai, R., & Fan, J. (2023). Progress on mechanisms of age-related hearing loss. *Frontiers in Neuroscience, 17*, Article 1253574.

Zhang, L., Chen, S., & Sun, Y. (2022). Mechanism and prevention of spiral ganglion neuron degeneration in the cochlea. *Frontiers in Cellular Neuroscience, 15*, Article 814891.