Title page

Manuscript title: The efficacy of statins as otoprotective agents: A systematic review

Short running head: Otoprotective effect of statins

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Conflicts of interest:

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Acknowledgment:

David Baguley is supported by the UK National Institute of Health Research (NIHR), but the views herein are his own, and do not reflect those of the NIHR nor the UK Department of Health and Social Care.

Data availability statement:

The datasets analysed in this manuscript are not publicly available. Requests to access the datasets should be directed to the corresponding author.

Abstract

Objective: This systematic review examined the current literature, summarized research findings and identified research gaps regarding the efficacy of statins on audiological outcomes.

Methods: Systematic search of electronic databases and grey literature was performed. Eligibility criteria was the study of a statin drug with report of audiological outcomes such as hearing, tinnitus, or balance in either human or animal studies. Data extraction and quality assessment were performed by two independently researchers. The characteristics of the study and research findings were collated and summarized. A narrative synthesis was conducted. Meta-analysis was not possible due to heterogeneity of the included studies.

Results: Analysis of searches yielded 17 studies meeting the criteria. Included studies had variable drug type and dosage, outcome measures, and associated inner ear conditions. Most animal experiments showed promising audiological outcomes after statin treatment, demonstrated by the results of auditory brain stem response, distortion product otoacoustic emissions, and inner ear histology. However, no clear effect can be discerned in human trials due to the mixed results, and heterogeneity in research methodology and quality. Audiological outcomes were not always correlated with cholesterol levels.

Conclusions: Statins remain a potential candidate as otoprotective agents which warrant further investigation.

Key words: Statins, Hydroxymethylglutaryl-CoA reductase inhibitors, Otoprotection, Hearing, Audiogram

Introduction

Inner ear impairment can be characterized by cochlear dysfunction or vestibular dysfunction or both (1). Sensorineural hearing loss (SNHL) has a high prevalence and can cause significant adverse impact on an affected individual's quality of life (2). The pathophysiological mechanisms involved in SNHL include vascular ischemia, oxidative stress, and inflammation (3).

Hyperlipidemia has been reported to be associated with sudden sensorineural hearing loss (SSNHL) (4), and noise-induced hearing loss (NIHL) (5). One possible explanation regarding the mechanism of hearing damage by dyslipidemia involves vascular ischemia of the inner ear artery. Hyperlipidemia increases plasma viscosity (6) which can trigger the stenosis of the cochlear artery leading to cochlear ischemia and subsequent SNHL; therefore, vascular compromise is regarded as playing a vital role in SNHL (7).

Hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitors, commonly known as statins, are widely used as cholesterol-lowering drugs (8). Due to the strong evidence supporting cardiovascular benefits of its usage, statin therapy to reduce high cholesterol is recommended for people with cardiovascular risk factors. The overall benefits observed with statins appear to be greater than what might be expected from changes in lipid levels alone, suggesting effects beyond cholesterol reduction such as improved endothelial function and microcirculation, reduced oxidative stress, and decreased inflammation (9).

The effect of statins, including the cholesterol lowering, anti-oxidative, and anti-inflammatory properties, could be beneficial as an otoprotective agent involving both hemodynamic and metabolic mechanisms. This is of interest because hearing loss associated with hyperlipidemia would be thereby potentially treatable. There has so far been little evidence to support their use in the treatment or prevention of inner ear dysfunction, hence statins are not routinely used for this purpose. This systematic review examined the current literature on the efficacy of statins on audiological outcomes.

Method

Identify relevant studies

The following databases were searched: Medline, EMBASE, IPA (International Pharmaceutical Abstracts), and ClinicalTrials.gov. Grey literature was also sought through the conference abstracts searching on Google Scholar.

The steps followed the PRISMA guideline (10). Standardised terms and keywords were merged in the search for concepts of statin drugs and otoprotection. Study details were registered on PROSPERO (CRD42019133701). The search was limited to the English language because of resource constraints. The search strategies are reported in Appendix 1.

Study selection

Eligibility criteria for records to be included was the study of a statin with reporting of audiological outcomes such as hearing, tinnitus or balance in either human or animal studies. All study types were eligible except review articles and *in vitro* studies. Two screening steps were undertaken independently by two authors. The first step checked that each title and abstract was within the scope of research question. The second step considered the eligibility criteria. Discrepancies were resolved through discussion.

Data extraction

Data from each included study was extracted independently by two clinical experts on the team (PP, an otorhinolaryngologist and DB, an audiologist) using a data extraction form. Pre-specified data items included study design, participant demographics, sample size, drug type and dosage, and outcome evaluation. Discrepancies were identified and resolved through discussion.

Quality assessment

The reviewers independently assessed the methodological quality of the articles by applying the National Institutes of Health (NIH) Quality Assessment Tool. If the ratings were different, then reviewers discussed the article in an effort to reach consensus. The score was assigned for each item: ‘Yes’ was scored 1, and ‘No’ or ‘Cannot determine’ or ‘Nor reported’ was scored 0. The summary score of each study was calculated, expressed as a percentage, and could range from 0% to 100%. These were categorized into four categories: poor (0–25%), fair (26–50%), good (51–75%) or excellent (76–100%). The quality score was not used as the criteria for eligibility because of the limited literature on this topic.

Data synthesis

A narrative synthesis was implemented for the present systematic review, as there were high heterogeneities of studies included. The characteristics of the study and research findings were collated and summarized.

Results

A summary of the study selection processes with the reasons for exclusion is represented in Figure 1. Seventeen individual studies were included for data extraction. The results are presented in a narrative summary and review. We did not perform a meta-analysis as the studies were heterogeneous, and several of them were observational designs.

Descriptions of included studies

Nine articles revealed human studies comprising of 1 RCT (11), 3 pre-post studies (12-14), 2 cohort studies (15, 16), 2 retrospective studies (17, 18), and 2 case reports (16, 19). Eight animal studies included 2 randomized studies (20, 21), and 6 non-randomized controlled interventional studies (22-27).

Quality assessment

The mean score on the NIH Quality Assessment Tool was 38% (range 7–79%). There were eight studies (47%) with fair quality; five studies (29%) had fair quality; three studies (18%) had good quality; and one study (6%) had excellent quality (See Table 1).

Human studies

Outcome measurements were highly variable among studies, and included audiometry (11-13, 15, 17-19), tinnitus questionnaire (11, 17), Tinnitus Handicap Questionnaire (THQ) (14), tinnitus degree/severity/loudness (13), self-reports of tinnitus (19), and vertigo symptoms (16). The summary of characteristics and results of included human studies are demonstrated in Table 1.

Two studies classified participants into responsive and unresponsive groups according to cholesterol levels after the treatment, and then compared the audiological outcomes (13, 14). The criteria for responsive and non-responsive individuals were substantially different. Cholesterol responsive was defined by a return to normal cholesterol or triglyceride level but normal levels were not specified (13), or cholesterol level less than 200 mg/dL (14).

Audiometry

Mixed results were reported with 2 studies concluding no improvement in hearing threshold (11, 17), and 4 studies reporting some improvement (12, 13, 18, 19). Two studies reported a correlation between statin use and a reduced prevalence of hearing loss (15, 18).

There was no significant difference in pure tone thresholds between atorvastatin and placebo groups (11). Another study reported no significant difference in hearing threshold between simvastatin and ginkgo groups (17).

Nine out of twelve (75%) patients with chronic-phase SSNHL had hearing improvement in at least 2 frequencies (12). There was a significant improvement of hearing threshold at higher frequencies in the cholesterol treatment responsive group compared to the unresponsive group (13). Patients on statins showed reduced severity of hearing loss than did non-statin users (18). A case report described a substantial hearing improvement after rosuvastatin therapy (19).

Gopinath et al (15) indicated that persons with self-reported statin use had a 48% reduced odds of hearing loss. Another study reported reduced incidence of hearing loss compared with pretreatment audiograms in statin users relative to individuals who were not on a concurrent statin therapy (18).

Tinnitus

Studies described varied results of no significant improvement of tinnitus (11, 17), and significant improvement (13, 14, 19).

There was a trend towards relief of tinnitus in the atorvastatin group while tinnitus severity scores were rather stable in the placebo group (11). In another study, there was no significant difference in tinnitus score between simvastatin and ginkgo groups (17).

There was a significant improvement of tinnitus intensity and self-rated tinnitus in cholesterol responsive group relative to cholesterol non-responsive group (13). Improvement in THQ score by at least 10 points was seen in 70.5% of patients in cholesterol responsive group compared to 4.2% in cholesterol unresponsive group (14). A case report described complete relief of tinnitus after statin therapy (19).

Vertigo

One article reported that 84% of vertiginous patients had complete resolution of vertigo and total remission in one case of recurrent vertigo after statin treatment (16).

Cholesterol level and audiological outcomes

Most patients who received statin treatment had elevated cholesterol levels ranging from 100-190 (11) to 239-356 (14) mg/dL. However, specified criteria of hyperlipidemia or cholesterol levels were not reported in some studies (13, 15, 16, 18).

Successful cholesterol lowering was associated with significant improvement of tinnitus (13, 14) and hearing threshold (13). Another two studies also showed parallel results of cholesterol lowering and hearing improvement (12, 19). On the other hand, two studies reported no audiological improvement despite cholesterol reduction after statin treatment (11, 17).

Animal experiments

Outcome measurements were highly variable among studies, and include auditory brainstem response (ABR) (20-22, 24-27), distortion product otoacoustic emissions (DPOAE) (21, 23, 24), and inner ear histology (20, 22, 25). The summary of characteristics and results of included animal studies are reported in Table 2.

ABR

Most of the included studies reported protection of hearing detected by ABR (20, 22, 24-27), except in one study (21).

Cai et al (20) found that hearing thresholds remained stable at 40 dB in simvastatin-treated mice fed with high-lipid diet while significant increased hearing thresholds from 35 dB to 60 dB was observed in the non-statin treated group. Three studies demonstrated the efficacy of statins to prevent NIHL (22, 26, 27). Park et al (22) revealed a significantly decreased hearing threshold shift of approximately 20 dB in the pravastatin-pretreated group of mice compared to the noise-only group at 1 and 14 days. ABR threshold after noise exposure was 5.83 dB in fluvastatin-treated mice, which was substantially lower than the 41.7 dB in the noise-only group (27). Another study reported that fluvastatin given 7 days before noise exposure can protect the inner ear against NIHL in the guinea pigs (26). Statin treatment prior to acoustic injury appeared to be more effective than when given after noise exposure (26). Only one study examined statin treatment in cisplatin ototoxicity, reporting that ABR thresholds were significantly protected in cisplatin-treated mice receiving prior lovastatin relative to cisplatin-only treated mice (24). Furthermore, hearing preservation was observed in diabetic mice treated with atorvastatin but without detailed information (25).

In contrast, there were no significant differences in hearing thresholds between atorvastatin-treated mice and control mice, but all animals had normal hearing threshold (21).

DPOAE

Three studies reported DPOAE results: all showed positive auditory outcomes of statin usage (21, 23, 24). Two of three studies reported both ABR and DPOAE outcomes (21, 24). The results were concordant in one study which demonstrated the preservation of both ABR threshold and DPOAE in the lovastatin treated group (24). Conversely, another study demonstrated better results of DPOAE in atorvastatin treated mice though no significant differences in hearing thresholds detected by ABR (21).

Inner ear histology

Three studies reported histological findings of the inner ear in animals (20, 22, 25). After statin administration, there was preservation of the numbers and morphology of hair cells and spiral ganglions in hyperlipidemic mice (20), and spiral ganglia and stria vascularis in diabetic mice (25). Conservation of hair cells were also demonstrated after noise exposure (22).

Cholesterol level and audiological outcomes

Hearing improvements corresponded to the results of cholesterol lowering in two studies (20, 22), but not related to cholesterol level in one study reported (21). Nonetheless, cholesterol levels were not reported in five studies (23-27).

Normal hearing findings, alongside lower cholesterol levels and much less severe atherosclerotic lesions in simvastatin-treated mice, support the role statin drugs play in the protection of hearing loss (20). Interestingly, the inner ear protection efficacy of statins was also found when cholesterol lowering effects were absent (21).

Discussion

Current literature regarding a potential otoprotective effect of statin drugs has high variability in drug type and dosage, outcome measures, and associated inner ear status. Most of the studies were classified to have fair or poor quality, and a significant portion of included studies retrieved from grey literature reported limited information.

Most animal experiments showed promising audiological results; however, no clear effect can be discerned from human trials. The differences between animal experiments and human studies are potentially due to the difference in species, equivalent drug dosage, and outcome measurements.

Drug type, dosage, and timing of administration

Statin type and dosage varied among studies. While, low dose atorvastatin used before exposure to noise can potentially prevent NIHL in rats, the effect was not observed in higher doses (23). Animal studies demonstrated a protective effect when the drug was administered before or during noise exposure but showed limited efficacy when given after noise exposure (22, 23, 26, 27). This could be explained by the pathophysiology of ROS production in that ROS is hard to overcome when it has occurred but prevention by diminishing the inflammatory process is more effective.

Outcome measures

Most of the animal experiments demonstrated favourable outcomes of ABR and DPOAE in statin-treated animals, supported by histological findings. The discrepancy between ABR and DPOAE results in Syka et al (21) can be explained by the different pathways and sensitivities of the tests. (28, 29).

Tinnitus evaluation varied highly among studies using self-reported symptoms and standard questionnaires which emphasizes the difficulty of comparison between studies.

Inner ear conditions

Tentative evidence was identified to support an otoprotective effect of statin against NIHL caused by acoustic overstimulation (13, 22, 23, 26, 27), and cisplatin ototoxicity (24). Interestingly, one accepted mechanism shared by these conditions is related to overproduction of ROS (30), supporting the proposal of an anti-oxidative effect of statin treatment. Statin treatment in patients with other SNHL and tinnitus showed mixed results with no benefits (11, 17, 21), and some benefits (12-15, 20, 25). Despite these mixed results of statin treatment, some reversibility of hearing loss and tinnitus was demonstrated in the chronic phase (12-14, 19).

Cholesterol level and audiological outcomes

Six studies showed positive audiological outcomes accompanied by lower cholesterol levels (12-14, 19, 20, 22), indicating cholesterol dependent effects of statin on audiological outcomes. These studies support the pathophysiology of vascular ischemia associated with hypercholesterolemia which leads to oxygen reduction, overproduction of ROS and an inflammatory process causing eventually to apoptotic cell death.

In contrast, three studies reported no correlation of inner ear functions and cholesterol lowering outcomes after statin treatment (11, 17, 21), signifying that hearing outcome may not be associated with cholesterol levels. Syka et al (21) showed some efficacy of inner ear protection after statin treatment with no effects on cholesterol levels, supporting the pleiotropic (cholesterol-independent) effects of statins (9).

No significant improvement of hearing thresholds and tinnitus were reported in two studies although they showed the successful cholesterol lowering effect of statins (11, 17). Olzowy et al (11) included only patients who had presbycusis with moderately elevated cholesterol levels and Canis et al (17) showed a relatively small change of cholesterol level. It is possible that patients with higher baseline cholesterol levels or who had a larger change of cholesterol level might have a pronounced benefit from statin treatment on cochlear functions.

Limitations of the study

Some limitations of the current review are that a significant portion of included studies reported limited information, and only publications in the English language were included; thus, language bias may have occurred.

Conclusion

Included studies had variable methodology and quality. Most animal experiments showed promising results; however, no clear effect was discerned from the results in human trials. Developing therapeutic strategies for the prevention of hearing loss using otoprotective drugs, is one of the major goals of current auditory research, and statins remain of interest in this regard.

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Figure 1: Flow chart of stages of the study selection process

Table 1: Summary data of human studies

OD = once daily; NR = not reported; THQ = Tinnitus Handicap Questionnaire; SSNHL = Sudden sensorineural hearing loss

Table 2: Summary data of animal experiments

ABR = Auditory brainstem response; DPOAE = Distortion Product Otoacoustic Emission; IP = Intraperitoneal; NR = not reported

Appendix 1: Search strategy

Table 1: Summary data of human studies

Study no.	Title	Sample size	Study population	Statin drug, dosage and duration	Outcome measures	Audiological outcomes
1	Effect of atorvastatin on progression of sensorineural hearing loss and tinnitus in the elderly: results of a prospective, randomized, double-blind clinical trial (11)	48	Adults with presbycusis	Atorvastatin 40 mg OD	- Audiometry - Tinnitus questionnaire	- Mean deterioration of hearing threshold of all ears in all dB in the atorvastatin and 1.07 dB in the placebo group. T significant difference between both groups. - Trend toward a reduction of tinnitus score but not signif Atorvastatin group: 38.3 -> 34.8 -> 27.6 Placebo group: 23.6 -> 24.8 -> 26.8
2	Hearing improvement after therapy for hyperlipidemia in patients with chronic-phase sudden deafness (12)	12	Adults with unilateral SSNHL	Pravastatin for 90-519 days	- Audiometry	- Nine patients had hearing improvement (> 10 dB) in mo - Mean hearing level had improved significantly at 125, 2
3	Low-Cholesterol Diet and Antilipid Therapy in Managing Tinnitus and Hearing Loss in Patients with Noise-Induced Hearing Loss and Hyperlipidemia (13)	42	Adults with subjective tinnitus and hearing loss due to noise exposure	Simvastatin 10-40 mg OD or Atorvastatin 10-80 mg OD for 1-2 years	- Audiometry - Tinnitus degree (1-10) - Tinnitus severity - Tinnitus loudness	Comparing cholesterol responsive (N=20) and unresponsi - Significant improvement of hearing threshold at 4,000 a significant difference at 500, 1,000, and 2,000 Hz in respo - Significant improvement of tinnitus degree and severity
4	Atorvastatin in the management of tinnitus with hyperlipidemias (14)	98	Adults with tinnitus and SNHL at least one year	Atorvastatin 40 mg OD for 8 weeks	- THQ	Comparing cholesterol responsive (N=51) and unresponsi - Improvement in tinnitus score in the responsive group w patients and in 2 (4.2%) patients of the unresponsive grou
5	Dietary intake of cholesterol is positively associated and use of cholesterol-lowering medication is negatively associated with prevalent age-related hearing loss (15)	274	Adults with presbycusis	Statins	- Audiometry	- Reduced odds of having impaired hearing among those both cross-sectionally and longitudinally. - Persons self-reporting statin use were 48% less likely to after multivariable adjustment [OR = 0.52; 0.29–0.93].
6	Vestibular vertigo associated with hyperlipidemia: response to antilipidemic therapy (16)	31 1	Adults with recurrent vertigo	Lovastatin or Pravastatin 20-40 mg/d	- Vertigo symptoms	- 84% of patients in a cohort had complete resolution of v - Total remission of vertigo and did not recur in a case rep
7	Simvastatin and Ginkgo biloba in the treatment of subacute tinnitus: a retrospective study of 94 patients (17)	94	Adults with moderate to severe tinnitus	Simvastatin 40 mg OD for 4 months	- Audiometry - Tinnitus questionnaire	- There was no significant difference in hearing threshold and ginkgo groups - There was no significant improvement in tinnitus scores Simvastatin group: 41.4 -> 37.3 Ginkgo group: 44.7 -> 41
8	Concurrent use of cholesterol lowering drugs may reduce the incidence of ototoxicity in cisplatin-treated patients (18)	NR	Adults received cisplatin chemotherapy	Lovastatin	- Audiometry	- A reduced incidence and severity of cisplatin-induced h users relative to individuals who were not on a concurren
9	Hearing loss due to familial hypercholesterolemia and statin treatment (19)	1	An adult with SSNHL, tinnitus and positional vertigo	Rosuvastatin 40 mg OD for 1 year	- Audiometry - Tinnitus status	- There was a substantial improvement of hearing test and of tinnitus.

OD = once daily; NR = not reported; THQ = Tinnitus Handicap Questionnaire; SSNHL = Sudden sensorineural hearing loss

Table 2: Summary data of animal experiments

Study no.	Title	Sample size	Study animals	Statin drug, dosage and duration	Outcome measures	Audiological outcomes
1	Effects of simvastatin on plasma lipoproteins and hearing loss in apolipoprotein E gene-deficient mice (20)	30	Mice	Simvastatin oral for 14 weeks	- ABR at 0.3-3 kHz - Histology	- Hearing thresholds remained stable at 40 dB in simvasta significant increased hearing thresholds from 35 dB to 60 group. - Preservation of hair cells and neurons in the spiral gangl treated group.
2	Atorvastatin slows down the deterioration of inner ear function with age in mice (21)	50	Mice	Atorvastatin oral 10 mg/kg/day for 8 weeks	- ABR at 0.3-10 kHz - DPOAE at 4-40 kHz	- All animals had normal hearing thresholds. - No significant differences in hearing thresholds betwee group and control group. - Larger amplitudes of DPOAE in atorvastatin treated wil at high frequencies (19 to 27 kHz).
3	Pravastatin attenuates noise-induced cochlear injury in mice (22)	29	Mice	Pravastatin oral 25 mg/kg/day for 5 days prior to noise exposure and/or 3 days after noise exposure	- ABR at 16 and 32 kHz - Histology	- Hearing thresholds were 43.2-47.4 dB in the noise-only dB in the pravastatin-pretreated group at 1 day after noise - Hearing thresholds were 41.9-45.9 dB the noise-only gr in the pravastatin-pretreated group at 14 days after noise - No increased attenuation of threshold shift when pravas administered after noise exposure, compared with the pre - Increase hair cells survival rate in statin-treated group.
4	The effect of atorvastatin on preventing noise-induced hearing loss: an experimental study (23)	40	Rats	Pretreatment atorvastatin oral 5, 25, and 50 mg/kg/day for 14 days	- DPAOE at 2-8 kHz	- Response amplitude was significantly decreased at all fr immediately after exposure to noise in all studied groups. - The amplitude increased after 72 hours to a level higher threshold shift (TTS); this change was only significant in mg/kg atorvastatin.
5	Protective effects of concurrent statin use against ototoxicity in cisplatin-treated mice (24)	NR	Mice	Lovastatin oral 40 or 60 mg/kg/day prior to cisplatin for 2 weeks	- ABR at 8-40 kHz - DPOAE at 8-40 kHz	- ABR response thresholds in the low to mid frequencies protected. - DPOAE were preserved, though reduced.
6	The effect of atorvastatin on hearing impairment in diabetic mice (25)	40	Mice	Atorvastatin 20 mg/kg IP every other day for 4 weeks	- ABR at 16 and 32 kHz - Histology	- There was a preservation of hearing. - There was a preservation of spiral ganglion neurons and
7	Fluvastatin attenuates acoustic injury (26)	NR	Guinea pigs	Fluvastatin 50 mM direct to Lt cochlea either 7 days before or after noise exposure	- ABR	- Fluvastatin given 7 days before can protect against NIH - Fluvastatin given 7 days after noise exposure was not as show a mild protection.
8	Fluvastatin protects against high decibel noise induced hearing loss (27)	24	Guinea pigs	Fluvastatin direct to Lt cochlea at the same time as noise exposure	- ABR	- ABR threshold elevation after exposure was 41.7±12 dB and 5.83±10.7 dB for noise exposed fluvastatin treated gr

ABR = Auditory brainstem response; DPOAE = Distortion Product Otoacoustic Emission; IP = Intraperitoneal; NR = not reported