Effect of Statins on Hearing Function and Subjective Tinnitus in Hyperlipidemic Patients

HILAL YÜCEL¹, ABITTER YÜCEL¹, HAMDI ARBAĞ², ERKAN CURE³, MEHMET AKIF ERYİLMAZ⁴, AHMET BEDRI ÖZER⁵

¹ Department of Otorhinolaryngology, Health Sciences University, Meram Education and Research Hospital, Konya, Turkey

² Department of Otorhinolaryngology Head and Neck Surgery, Necmettin Erbakan University, Konya

³ Department of Internal Medicine, Camlica Erdem Hospital, Uskudar, Istanbul, Turkey.

⁴ Department of Otorhinolaryngology Head and Neck Surgery, Necmettin Erbakan University, Konya, Turkey.

⁵ Department of Otorhinolaryngology Head and Neck Surgery, Medicana International Hospital, İstanbul, Turkey

Running head: Effects of statins on hearing and tinnitus
ABSTRACT

Introduction: It is known that hyperlipidemia reduces hearing functions. In this study, we aimed to study the effect of antihyperlipidemic drugs on hearing functions and tinnitus.

Methods: Eighty-four patients aged 18 to 84, who were diagnosed with hyperlipidemia and started treatment with the statin group (atorvastatin 20 mg and 40 mg, rosuvastatin 10 mg and 20 mg, and simvastatin 20 mg) of antihyperlipidemic drugs, were included in this study. All patients underwent pure-tone audiometry before starting treatment with antihyperlipidemic drugs. Patients with tinnitus were evaluated by Tinnitus Severity Index and Visual Analogue Scale. In the 6th month of the therapy, otologic examination, pure-tone audiometry and tinnitus evaluation of the patients were repeated.

Results: No significant difference was found in the pure-tone averages of the patients before and after statin use (p>0.05). However, it was found in the audiometry that, after statin use, all drugs caused to statistically significant decrease in the hearing thresholds at 6000 Hertz (p<0.05). Also, strongly increase was found in the Speech Discrimination percentages after treatment in patients using rosuvastatin 10 mg (p= 0.022). A significant decrease was found in the tinnitus frequency, duration, severity and degree of annoyance in patients using rosuvastatin 10 mg and 20 mg (p<0.05).

Conclusion: Statin group of drugs can have a positive effect on the hearing functions and subjective tinnitus. In particular, it is seen that rosuvastatin group of statins has a more notable effect on tinnitus. It was considered that further studies with larger patient groups are needed.

Keywords: Statin, rosuvastatin, hyperlipidemia, subjective tinnitus, hearing loss
INTRODUCTION

Hyperlipidemia plays a significant role in the pathogenesis of cardiovascular diseases, cerebrovascular diseases, and peripheral vascular diseases, which are among the leading causes of mortality and morbidity across the world [1]. Aside from these effects, hyperlipidemia may also lead to microcirculation disorders in the hearing system and have a negative effect on the hearing functions, therefore causing tinnitus [2].

Effects of the drugs used in the treatment of hyperlipidemia on hearing functions and tinnitus were studied in various animal and clinical trials. It is argued that, especially, these effects of the statin group of drugs, competitively inhibiting the 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-COA reductase), which is the rate-limiting step in the cholesterol synthesis, are associated with a decrease in plasma viscosity and the epithelium-derived nitric oxide (NO) vasodilation [3,4]. On the other hand, loss of flexibility in the lateral membranes of cochlear outer hair cells due to hyperlipidemia and the resulting functional disorders can be eliminated by an effective decrease in the cholesterol level [2]. Therefore, it is suggested that pathologies such as hearing loss and tinnitus in especially patients of advanced age can be treated or reduced with the statin group of drugs, which are, again, used mostly in this age group.

Tinnitus severity of the patients should be evaluated before treating tinnitus. Tinnitus handicap questionnaire [5], tinnitus severity index [6] and tinnitus handicap inventory [7] are used for this evaluation. Even though all these questionnaires are a reliable source for tinnitus severity, the easiest one in terms of briefness is the tinnitus severity index. Therefore, we used the tinnitus severity index in our study.

In this study, we aimed to study the effect of the statin group of drugs on hearing functions and subjective tinnitus by using hearing tests and tinnitus severity index.
MATERIAL AND METHODS

Patients selection and study design

Eighty-four patients aged 18 to 84, who were diagnosed with pure hyperlipidemia and received treatment with statin group of drugs between 2012 and 2013, were included in this prospective, observational, drug study. Ethical approval was obtained from the Local Ethics Committee of The University for this study. Lipid values, ear examinations and tinnitus screenings of the patients were made before starting and at the 6th month of the treatment.

Patients who did not have any systemic cerebrovascular disease, diabetes mellitus, hypertriglyceridemia (triglyceride ≥400 mg/dl) and any middle ear or external auditory canal pathology and did not receive any medical treatment related to tinnitus, and whose tympanic membrane was intact during otologic examination, were included in this study. Also, tympanometry test was made for each patient after otologic examination (AZ26 Impedance Audiometer, Interacoustic Company, Denmark). Those with pathological tympanometry were excluded from the study. Patients using ototoxic drugs were not included in the study. Patients using atorvastatin 20 mg (A20), atorvastatin 40 mg (A40), rosuvastatin 10 mg (R10), rosuvastatin 20 mg (R20) and simvastatin 20 mg (S20) were included in the study.

Laboratory measurements

Total cholesterol (TC), triglyceride (TG), high density lipoprotein (HDL), low density lipoprotein (LDL) values of all patients attending the study were recorded before and at the 6th month of the treatment. The frozen serum samples were thawed and mixed well before biochemical analysis. Serum activities of total cholesterol, triglyceride, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol were measured by using standard autoanalyzer methods on Abbott Architect 16000 system with the original reagents according to the manufacturer’s instructions (Abbott Laboratories, Abbott Park, IL, USA).

Otologic Examination
Pure-tone audiometry test was made for all patients before starting to use statin and at the 6th month of the treatment. Audiometric measurements were made with AC-33 (interacoustics clinic, Denmark). In pure-tone audiometry, pure-tone averages, 250-6000 Hz bone conduction thresholds and 250-8000 Hz air conduction thresholds, speech reception thresholds, speech discrimination percentages of the patients were evaluated. Patients with Total sensorineural hearing loss and conductive hearing loss were not included in the study. Patients with asymmetrical hearing loss were evaluated by imaging methods in terms of inner ear pathology.

While patients with objective tinnitus were excluded from the study, patients with subjective tinnitus were evaluated physically, emotionally and socially by tinnitus severity index before starting to use the drug and at the 6th month of drug use. As a result of a 12-question survey, tinnitus symptom scores (TSS) were calculated. TSS of 1 to 12 were classified as slight, 13 to 24 as mild, 25 to 36 as moderate, 37 to 48 as severe, 49 to 60 as catastrophic tinnitus [8]. Also, tinnitus severity, frequency and duration of tinnitus, and patient's level of annoyance were examined by visual analogue scale (VAS). The patient was asked to assign a value between 0 (none) and 10 (excruciating) related to the severity, frequency and duration of the ringing and the level of annoyance and these parameters were evaluated. A score of 2 and over was considered as significant in the VAS scoring.

Statistical analysis

Results were given as mean ± standard deviation. Statistical analysis was carried out by SPSS package program (version 18, IBM, Chicago, IL, USA). Audiometric measurements, TSS and VAS scores of the patients in months 0-6 were compared by the paired T test. Post-treatment effects of the drugs on the decreases in lipid were evaluated by using the Mann Whitney U test. Pearson correlation test was used for the correlation analysis. A p value less than 0.05 was considered as significant.
RESULTS

Patient characteristics

Of the 84 people attending the study, 45 were women and 39 were men. The mean age of the patients was 60 while the median was 61 (min: 27, max: 80). 48 of the patients had hypertension, and 40 had coronary artery disease; while 39 of these patients were using aspirin (Table 1). Among all patient groups using statin, there was no statistically significant difference in terms of gender, hypertension, coronary artery disease, and aspirin use and body mass index (p>0.05).

Lipid parameters

Twenty-six, 13, 17, 19 and 9 of the 84 patients attending the study used A20, A40, R10, R20 and S20, respectively. When the pre- and post-treatment cholesterol levels were examined, a notable decrease in TC (233.5±15.9 mg/dl vs. 202.1±24.5 mg/dl, p<0.001), TG (237.1±17.8 mg/dl vs. 216.6±18.7 mg/dl, p<0.001), LDL (149.9±9.3 mg/dl vs. 117.6±21.2 mg/dl, p=0.002) values, and significant increase in HDL value (36.2±6.1 mg/dl vs. 41.1±6.5 mg/dl, p<0.001) were identified compared to pre-treatment values. When post-treatment increase and decrease in cholesterol levels versus antihyperlipidemic agents were examined; A20, A40, R10, R20, S20 decrease in TC was, respectively, 8.5±5.1%, 18.4±5.7%, 12.2±6.3%, 5.2±3.4%; decrease in TG 8.6±3.4%, 7.8±2.1%, 9.0±2.2%, 10.5±4.3%, 5.0±2.5%; decrease in LDL 13.8±7.4%, 29.2±8.0%, 19.6±10.0%, 34.4±15.0%, 8.8±4.5%. R20 decreased significantly more than A20 (p<0.001), R10 (p<0.001), and S20 (p<0.001) in LDL value. A40 decreased more than A20 (p<0.001), R20 (p<0.011), and S20 (p<0.001) in LDL value. R10 was also more active than S20 (p=0.011). The percentage of increase in HDL cholesterol was, respectively, A20 11.6±4.4%, A40 10.4±7.4%, R10 12.8±3.4%, R20 14.5±3.5%, S20 8.9±3.3%. R20 increased more than A20 (p=0.040), A40 (p=0.016), S20 (p=0.004) in HDL levels. R10 increased its HDL value more than S20 (p=0.043).
Audiometric measurements

In audiometric measurements before drug use of patients, pure-tone averages were 21.83 dB in the left ear and 21.86 dB in the right ear. After drug use, pure-tone averages were 22.2 dB in the left ear and 22.54 dB in the right ear. There was no statistically significant difference in terms of pure-tone averages for both ears in months 0-6 (p >0.05). After drug use, changes in both ears were similar. Among the patients using statin the least change in pure-tone averages in months 0-6 occurred in patients using R10. A decrease of about 0.1 dB for the right ear and a decrease of around 0.5 dB for the left ear was found in pure-tone average. However, this decrease was not statistically significant and it is also not clinically significant difference (p>0.05) (Table 2).

There was not a statistically significant difference at speech reception thresholds of the patients during pre- and post-drug use period but a statistically significant increase was found in pre- and post-treatment Speech Reception Thresholds in the left ear for the group using A40 (p=0.019) (32.3-64.2) (Figure 1) (Table 2). When pre- and post-drug use Speech Discrimination Percentages were compared, no statistically significant difference was found in the statin groups other than R10; while a statistically significant increase was seen in Speech Discrimination percentages in both right (p=0.022) and left ear (p=0.012) in patients using R10 (Table 2). When the hearing thresholds were evaluated in terms of frequencies, no statistically significant difference was found in the pre- and post-statin use threshold levels at 4000 Hz and lower frequencies in bone conduction thresholds, while there was statistically significant improvement in both ears at 6000 Hz (right ear p=0.003, left ear p=0.017) (Figure 2) (Table 2). However, there was no statistically significant difference between the statin groups in terms of improvement on hearing levels for both ears at 6000 Hz in months 0-6 (p>0.05).

Correlation analysis
In the correlation analysis between TC, TG, HDL and LDL and audiometry hearing frequency levels; there was negative correlation in hearing levels between HDL month 0 level and left ear 4000HZ month 0 (r=-0.299, p=0.006), left ear 4000HZ month 6 (r=-0.329, p=0.002), right ear 4000HZ month 0 (r=-0.310, p=0.004), right ear 4000HZ month 6 (r=-0.318, p=0.003), left ear 6000HZ month 0 (r=-0.242, p=0.027), left ear 6000HZ month 6 (r=-0.245, p=0.025), right ear 6000HZ month 6 (r=-0.284, p=0.009). There was negative correlation in hearing levels between HDL month 6 level and left ear 4000HZ month 0 (r=-0.320, p=0.003), left ear 4000HZ month 6 (r=-0.341, p=0.001), right ear 4000HZ month 0 (r=-0.315, p=0.003), right ear 4000HZ month 6 (r=-0.324, p=0.003), left ear 6000HZ month 0 (r=-0.247, p=0.023), left ear 6000HZ month 6 (r=-0.251, p=0.021), right ear 6000HZ month 6 (r=-0.271, p=0.013). There was positive correlation in hearing levels between LDL month 0 level and left ear 4000HZ month 6 (r=0.243, p=0.026), right ear 4000HZ month 0 (r=0.306, p=0.005), right ear 4000HZ month 6 (r=0.298, p=0.006), left ear 6000HZ month 6 (r=0.225, p=0.040), and right ear 6000HZ month 6 (r=0.266, p=0.014). There was positive correlation in hearing level between LDL month 6 level and right ear 4000HZ month 0 (r=0.228, p=0.037). There was positive correlation in hearing levels between TG month 0 level and right ear 4000HZ month 0 (r=0.232, p=0.034) and right ear 4000HZ month 6 (r=0.236, p=0.031).

**Evaluation of tinnitus**

Twenty-four of the 84 patients attending the study had tinnitus. 13 of the patients who had tinnitus were women while 11 were men. 13 of the patients with tinnitus had bilateral tinnitus while 7 had in the left ear, and 4 in the right ear. Tinnitus severity of the patients was evaluated by the tinnitus severity index while their tinnitus frequency and duration were evaluated by VAS scoring.
While tinnitus symptom scores were similar before and after drug use, when they were evaluated based on types of drugs, statistically significant decrease occurred in tinnitus symptom scores in patients using A20, R10 and R20 (around 1 point) (p=0.036, p=0.005, p=0.002). Also, a positive redistribution was seen in tinnitus symptom scores after drug use (Table 3). Tinnitus frequency and duration were similar before and after drug use; but when they were compared based on types of drugs, a statistically significant decrease was observed in patients using A20 and R20 after treatment (p=0.014, p=0.039).

Tinnitus severity and level of annoyance due to Tinnitus were similar before and after drug use, but a statistically significant decrease was seen in tinnitus severity and level of annoyance after drug use both in R10 and R10. (Severity was, respectively, p=0.009, p=0.001, and level of annoyance was, respectively, p=0.005, p=0.001).

DISCUSSION

Hyperlipidemia is a critical condition that has an effect on both macrovascular and microvascular structures, affecting millions of people across the world, and causing serious consequences when untreated. Hyperlipidemia can have a negative effect on the hearing functions and therefore cause tinnitus since it causes increased blood viscosity, cochlear microcirculation disturbance as a result of decreased NO synthesis in microvascular bed, and reduced motility of cochlear outer hair cells [4,9,10]. Thus, the role of hyperlipidemia frequently encountered diseases, especially in the last periods, such as sudden hearing loss, presbyacusis and tinnitus are studied and various methods of treatment are tried. Canis et al. [11] have carried out LDL apheresis with fibrinogen for patients who do not benefit from steroid and plasma expander due to sudden hearing loss and identified complete or partial remission in the pure-tone average of 61% of the patients at the end of the 2nd week. Suckfull [12] has compared standard steroid treatment with LDL fibrinogen apheresis in 201 patients
with sudden hearing loss and less significant (1.8 dB) improvement was found in the hearing levels of healthy ear in patients who underwent apheresis.

High plasma cholesterol levels are among the most important risk factors in the development of hearing loss. In the potential mechanism for hyperlipidemia-related hearing loss, vascular changes such as increased blood viscosity and atherosclerosis as well as increased hardening of inner ear cells due to cholesterol uptake may cause hearing loss [13]. Low HDL and high LDL cause acceleration of the atherosclerotic process and disturbance in the vascular endothelial structure. The current study found a negative correlation between hearing levels at 4000 and 6000 Hz with HDL, and a positive correlation with LDL.

HMG-CoA Reductase inhibitors (Statins) used in the treatment of hyperlipidemia are often used worldwide for reducing blood cholesterol levels, and preventing hyperlipidemia-related atherosclerotic and ischemic diseases [4,14-16]. In this study, considerable improvements were detected in all cholesterol parameters of the patients with the 6-month statin use. Even though this change was significant in all statin groups, increase in HDL level and decrease in LDL level were more explicit in the groups using R20 and A40 than other statins. However, despite an improvement in all statin groups at 6000Hz in the audiometry, there was no statistically significant difference between statin groups in terms of improvement at this frequency. Independently of their cholesterol-lowering effects, statins affect vascular endothelium and increase NO synthesis, decrease blood viscosity and regulates cochlear microcirculation through angiotensin 1 receptors [4,14-16]. These observations give rise to the thought that, with statin use, microvascular effects of hyperlipidemia can be reduced and thrombotic and fibrinolytic balance in the cochlea can be directly regulated [17]. In an experimental study on a mouse with 25 Apo E gene defect, it was stated that simvastatin prevents side effects of hyperlipidemia on cochlea and can be used in hyperlipidemia-related
sensorineural hearing losses [18]. Syka et al. [19] suggested as a result of an experimental study on 34 mice that atorvastatin could slow down presbyacusis-related hearing loss in mice.

Olzowy et al. [20] studied the effect of Atorvastatin in elderly patients on hearing loss and tinnitus and found no statistically significant change in hearing thresholds. In our study, there was no statistically significant difference in hearing averages at 4000 Hz and lower frequencies before and after drug use. However, a statistically significant improvement of approximately 2 dB was found at hearing thresholds after statin use at 6000 Hz. But this difference was too small to be clinically significant and also this result could be due to the audiometry technician or patient. On the other hand, no significant change was found in Olzowy's study concerning speech discrimination levels of the patients, while in our study, a statistically significant increase was seen in both ears in patients using R10. Also, a statistically significant increase was found in speech reception thresholds in the group using A40 before and after treatment in the left ear.

However, there are reports that statins might have negative effects on hearing. In a study by Chung SD et al.[21] which is examining the relationship between sudden sensorineural hearing loss(SSNHL) and statin use, they compared 1263 patients with SSNHL and 6315 control groups (compatible with age and comorbidity) in terms of previous use of statins. They detected a statistically significant relationship between SSNHL and previous statin use, regardless of whether statin is used regularly. Lui M et al.[22] reported a progressive and irreversible hearing loss in a 32-year-old male patient after atorvastatin treatment at 18 months. The patient described recurrent and spontaneously recovering hearing loss six months after the start of treatment. In this period, the patient's audiometry was normal, but than bilateral cookie-bite, middle-frequency hearing loss was detected in the 18th month audiometry. A possible (2-point) temporal and causal relationship between the patient's hearing loss and atorvastatin was detected in the Naranjo adverse reaction drug reaction. In
our study, no statistically significant decrease was observed at patients in terms of hearing. But we followed up the patients only for 6 months. Long-term adverse effects may occur in these patients. Therefore, it may be necessary to follow these patients for a longer period. New studies are needed at this topic.

Neurons are highly sensitive to cholesterol changes created by statins and are much more permeable to lipophilic statins. Simvastatin is one of the best statins in maintaining neuropathological conditions with higher potential access to the central nervous system and have a good safety profile [23]. In our study, there was no evidence that simvastatin had a better outcome than other statins in terms of hearing.

Tinnitus affects about one fifth of the general public and one in three of the elderly population and is seen in the ages from 40 to 80 [24]. While many factors have been blamed for the pathophysiology and causes of tinnitus, its etiology has not been completely elucidated [25]. Several causes, including hearing losses, drug use, hypertension, and hyperlipidemia are blamed for the development of tinnitus. Hypertension and atherosclerosis are effective on the central nervous system microvascularity and cause high pitched subjective non-vibratory tinnitus that changes depending on blood pressure [26]. In this study, which is an observational drug study, the patient population was hyperlipidemic patient group; average age was 60 and tinnitus incidence was 29%. In our study, 16 of the patients with hypertension had tinnitus (33%), but a significant correlation could not be found between hypertension and tinnitus.

It has long been known that some groups of drugs, particularly aspirin, can cause hearing loss and tinnitus. Guitton et al. [27] found that aspirin disrupts the molecular structure of the outer hair cells, influences NMDA (N-Methyl-D-aspartate) receptors, and cause tinnitus. In our study, 11 of the patients using aspirin (%28) had tinnitus, but a significant relationship between tinnitus and aspirin use could not be found. Even though aspirin and
hypertension are considered among the factors causing tinnitus, there is no certain information in the literature concerning the incidence of tinnitus in patients using aspirin or those with hypertension. In our study, 18 of the patients with tinnitus (75%) had TSHL at high frequencies in the audiometry. This supports the view that there is a serious relationship between tinnitus and hearing loss, and both are the symptoms of the same process. Also, the fact that statins have positive effects on TSHL at high frequencies give rise to the thought that both pathologies can be positively influenced by Statin treatment.

In the retrospective study by Canis et al. [2], there was positive redistribution in Tinnitus symptom scoring in patients using 40 mg simvastatin, but statistically, significant change has not been observed. In another study, it has been reported that there was an improvement of tinnitus scores in 70% of the patients, whose serum cholesterol level returned to normal level after daily use of A40 [28]. In our study, both a significant decrease and a positive redistribution in tinnitus symptom scores were found in our patients after drug use. Also, tinnitus severity and level of annoyance from tinnitus decreased significantly after treatment in the patient group using R10 and R20. In the light of these results, it can be said that statin group of antihyperlipidemic drugs have positive effects on tinnitus, in addition to their cholesterol-lowering effects.

**STUDY LIMITATIONS**

We have planned this study prospectively at a limited time so the number of patients in the study groups was low. In addition, the distribution between the groups was not very homogeneous. Another limitation was hearing tests used in this study. Especially, if high frequency audiometry and autoacoustic emission tests were used, the change in hearing could have been more precisely determined.
CONCLUSION

In conclusion, there have been several studies in the literature related to the effect of statin group of drugs on hearing functions and subjective tinnitus, but multiple statin groups have not been included in any study as in ours. In this study, it has been shown that especially atorvastatin and rosuvastatin group of drugs have positive effects on hearing and tinnitus. Both hearing losses and tinnitus are seen more often in the advanced age group of patient population in particular, and the antihyperlipidemic drugs such as statin that are, again, used more often in the same population can lead to positive results for both clinical conditions.

Introducere: Este cunoscut faptul că hiperlipemia reduce funcția auditivă. Acest studiu are ca scop evaluarea efectului terapiei hipolipemiante asupra funcției auditive și a tinitusului.

Materiale si metode: Au fost recrutați 84 de pacienți cu vârste între 18 și 84 de ani, diagnosticați cu hiperlipemie și care au început tratamentul cu statine (atorvastatin 20 mg și 40 mg, rosuvastatin 10 mg și 20 mg și simvastatin 20 mg). Toți pacienții au făcut audiogramă înaintea înrolării în studiu. Pacienții cu tinnitus au fost evaluați cu scara vizuală analogă și cu indexul de severitate al tinitusului. După 6 luni de terapie pacienții au fost reevaluați.

Rezultate: Nu s-a observat niciodată diferență semnificativă statistic între tonurile recunoscute înainte și după folosirea statinelor. Totuși pragul de audibilitate a scăzut la 6000 Hertz după tratamentul cu statine. S-a observat o scădere a frecvenței, duratei, severității și percepției a tinitusului la pacienții care au primit rosvastatină de 10 și 20 mg.

Concluzii: Statinele pot avea un efect pozitiv asupra funcției auditive și asupra tinitusului. De subliniat este influența rosvastatinei la pacienții cu tinnitus. Sunt necesare studii ulterioare mai mari pentru a lămuri acest efect.

Correspondece to: Abitter Yucel, M.D, Assistant Professor, Department of Otorhinolaryngology, Health Sciences University, Meram Education and Research Hospital, Konya, Turkey.

Email: abitteryucel@hotmail.com

Tel: +90 505 267 71 46 Fax: +90 332 221 00 00

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.
REFERENCES

1. FOX KM., WANG L., GANDRA SR., QUEK RG., LI L., BASER O. Clinical and economic burden associated with cardiovascular events among patients with hyperlipidemia: a retrospective cohort study. BMC Cardiovasc Disord. 2016;16:13.

2. CANIS M., OLZOWY B., WELZ C., SUCKFULL M., STELTER K. Simvastatin and Ginkgo biloba in the treatment of subacute tinnitus: a retrospective study of 94 patients. Am J Otolaryngol. 2011;32(1):19-23.

3. MARON DJ., FAZIO S., LINTON MF. Current perspectives on Statins. Circulation. 2000;18;101(2):207-13.

4. FERON O., DESSY C., DESAGER JP., BALLIGAND JL. Hydroxy-methylglutaryl-coenzyme A reductase inhibition promotes endothelial nitric oxide synthase activation through a decrease in caveolin abundance. Circulation. 2001;103(1):113-8.

5. KUK FK., TYLER RS., RUSSEL D., JORDAN H. The psychometric properties of a tinnitus handicap questionnaire. Ear Hear. 1990;11(6):434-45.

6. MEIKLE MB., GRIEST SE., STEWART BJ., PRESS LS. Measuring the negative impact of tinnitus: A brief severity index. Abstr Assoc Res Otolaryngol. 1995;167.

7. NEWMAN CW., JACOBSON GP., SPITZER JB. Development of the Tinnitus Handicap Inventory. Arch Otolaryngol Head Neck Surg. 1996;122(2):143-8.

8. JERGER J., JERGER S. Measuring of hearing in adults, In paparella MM, Shumrick DA, eds, Otolaryngology, 2nd ed, Philadelphia 1980;1226.

9. NGUYEN TV., BROWNELL WE. Contribution of membrane cholesterol to outer hair cell lateral wall stiffness. Otolaryngol Head Neck Surg. 1998;119(1):14-20.

10. CANIS M., SCHMID J., OLZOWY B., JAHN K., STRUPP M., BERGHAUS A., et al. The influence of cholesterol on the motility of cochlear outer hair cells and the motor protein prestin. Acta Otolaryngol. 2009;129(9):929-34.
11. CANIS M., HEIGL F., SUCKFUEL M. Fibrinogen/LDL apheresis is a promising rescue therapy for sudden sensorineural hearing loss. Clin Res Cardiol Suppl. 2012;7:36-40.

12. SUCKFULL M. Fibrinogen and LDL apheresis in treatment of sudden hearing loss: a randomised multicentre trial. Lancet. 2002;360(9348):1811-7.

13. PARK JS., KIM SW., PARK K., CHOUGN YH., JOU I., PARK SM. Pravastatin attenuates noise-induced cochlear injury in mice. Neuroscience. 2012;208:123-32.

14. BRECHTELSBAUER PB., NUTTALL AL., MILLER JM. Basal Nitric Oxide production in regulation of cochlear blood flow. Hear Res. 1994;77(1-2):38-42.

15. GLORIOSO N., TROFFA C., FILIGHEDDU F., DETTORI F., SORO A., PARPAGLIA PP., et al. Effect of the HMGCoA reductase inhibitors on blood pressure in patients with essential hypertension and primary hypercholesterolemia. Hypertension. 1999;34:1281-6.

16. VAUGHAN CJ., GOTTO AM., BASSON CT. The Evolving Role of Statins in the Management of atherosclerosis. J Am Coll Cardiol. 2000;35(1):1-10.

17. BORGHI C., MODUGNO C., PIRADDA A. Possible Role of HMG-COA Reductase inhibitors for the treatment of sudden sensorineural hearing loss (SSHL). Med Hypotheses. 2002;58(5):399-402.

18. CAI Q., DU X., ZHOU B., CAI C., KERMANY MH., ZHANG C., et al. Effects of Simvastatin on plasma lipoproteins and hearing loss in apolipoprotein E gene–deficient mice. ORL J Otorhinolaryngol Relat Spec. 2009;71(5):244-50.

19. SYKA J., OUDA L., NACHTIGAL P., SOLICHIOVA D., SEMECKÝ V. Atorvastatin slows down deterioration of inner ear function with age in mice. Neurosci Lett. 2007;411(2):112-6.

20. OLZOWY B., CANIS M., HEMPEL JM., MAZUREK B., SUCKFULL M. Effect of atorvastatin on progression of sensorineural hearing loss and tinnitus in the elderly. Otol Neurotol. 2007;28(4):455-8.
21. CHUNG SD., CHEN CH., HUNG SH., LIN HC., WANG LH. A population-based study on the association between statin use and sudden sensorineural hearing loss. Otolaryngol Head Neck Surg. 2015;152(2):319-25.

22. LIU M., ALAFRIS A., LONGO AJ., COHEN H. Irreversible atorvastatin-associated hearing loss. Pharmacotherapy. 2012;32(2):e27-34.

23. SİERRA S., RAMOS MC., MOLİNA P., ESTEO C., VÁZQUEZ JA., BURGOS JS. Statins as neuroprotectants: a comparative in vitro study of lipophilicity, blood-brain-barrier penetration, lowering of brain cholesterol, and decrease of neuron cell death. J Alzheimers Dis. 2011;23(2):307-18.

24. MELO JJ., MENESES CL., MARCHIORI LL. Prevalence of tinnitus in elderly individuals with and without history of occupational noise exposure. Int Arch Otorhinolaryngol. 2012;16(2):222-5.

25. MOLLER AR. Pathophysiology of Tinnitus. Ann Otol Rhinol Laryngol. 1984;93:39-44.

26. PEIFER KJ., ROSEN GP., RUBIN AM. Tinnitus; Etiology and management, Clin Geriatr Med. 1999;15(1):193-204.

27. GUITTON M., CASTON J., RUEL J., JOHNSON R. Salicylate induces tinnitus through activation of cochlear NMDA receptors. J Neurosci. 2003;23(9):3944-52.

28. HAMEDD MK., SHEIKH ZA., AHMED A., NAJAM A. Atorvastatin in the management of tinnitus with hyperlipidemias. J Coll Physicians Surg Pak. 2014;24(12):927-30.

Received 18 September 2018
Figure 1. Changes of Speech Reception Thresholds (SRT) for Left Ear before and after treatment,
Figure 2. Changes of right and left ear hearing levels at 6000 Hz according to the statin groups before and after treatment

Table 1. Age, gender, comorbidity, co-medication, tinnitus status and type of statin for Patients.

| Age (years) (median [range]) | 61 (27-80) |
|-----------------------------|------------|
| Gender (M/F) (n)            | 39/45      |
| Tinnitus status(Patient with/without) | 24/60     |
| Hypertension (n,%)          | 48 (57.1)  |
| Coronary artery disease (n,%) | 40 (47.6) |
| Diabetes mellitus (n,%)     | 0 (0.0)    |
| Atorvastatin 20 mg (n,%)    | 26 (30.9)  |
| Atorvastatin 40 mg (n,%)    | 13 (15.4)  |
| Rosuvastatin 10 mg (n,%)    | 17 (20.2)  |
| Rosuvastatin 20 mg (n,%)    | 19 (22.6)  |
| Simvastatin 20 mg (n,%)     | 9 (10.7)   |
| Acetyl salicylic acid (n,%) | 39 (46.4)  |
**Table 2.** Pure Tone Averages, Speech Reception Thresholds, Speech Discrimination Percentages and hearing levels of 4000 and 6000 Hz on audiometry of all statin groups in values of baseline and after treatment.

|                  | Right Ear           |               | Left Ear           |               |
|------------------|---------------------|---------------|--------------------|---------------|
|                  | 0. month (dB)       | 6. month (dB) | 0. month (dB)      | 6. month (dB) |
| **All statin groups** | 21.86               | 22.54*        | 21.83              | 22.20‡        |
| **PTA**          | 37.50               | 37.38*        | 38.10              | 37.80‡        |
| **4000Hz**       | 48.69               | 46.67*        | 49.40              | 47.02‡        |
| **6000Hz**       | 31.37               | 31.33*        | 30.24              | 34.55‡        |
| **SRT**          | 84.14               | 84.33*        | 84.48              | 85.02‡        |

**Abbreviations:** PTA, pure tone averages; SRT, speech reception thresholds; SDP, speech discrimination percentages; dB, decibel.

* $p>0.05$ baseline values vs. after 6 months statin therapy.
‡ $p>0.05$ baseline values vs. after 6 months statin therapy.

**Table 3.** Distribution of Tinnitus Symptom Scores before and after statin use

| Tinnitus Symptom Score (TSS) | Before Statin Use (n) | After Statin Use (n) |
|-----------------------------|-----------------------|----------------------|
| Without Tinnitus symptom    | 60                    | 60                   |
| Very mild                   | 0                     | 4                    |
| Mild                        | 3                     | 8                    |
| Middle                      | 17                    | 9                    |
| Serious                     | 4                     | 3                    |
| Catastrophic                | 0                     | 0                    |
| Number of patients with Tinnitus | 24                  | 24                   |