ORIGINAL ARTICLE

Atorvastatin in the Management of Tinnitus with Hyperlipidemias

Mirza Khizer Hameed[1], Zeeshan Ayub Sheikh[1], Azeema Ahmed[2] and Atif Najam[1]

Abstract

Objective: To determine the role of atorvastatin in management of tinnitus in patients with hyperlipidemia.
Study Design: Quasi-experimental study.
Place and Duration of Study: ENT Department, Combined Military Hospital, Rawalpindi, from July 2011 to August 2012.
Methodology: Ninety eight patients of tinnitus with sensorineural hearing loss having hyperlipidemia were included in the study. Their pre-therapy serum cholesterols were measured, and tinnitus scores were recorded on a 'Tinnitus handicap questionnaire'. They were administered tablet atorvastatin 40 mg once daily with low fat diet for 8 months. After 8 months of therapy, patients were purposefully divided into responsive and unresponsive group depending on serum cholesterol levels. Post therapy serum cholesterol levels and tinnitus scores were also recorded after 8 months and compared with pre-therapy records.
Results: Serum cholesterol came to within normal limits in 51 (52%) patients (responsive group), while it remained high in 47 (48%) patients (unresponsive group). Improvement in tinnitus score in the responsive group was seen in 36 (70.5%) patients and in 2 (4.2%) patients of the unresponsive group. Improvement in tinnitus scores was compared in the two groups using Fisher's exact test and were found to be statistically better in the responsive group ($p < 0.001$).
Conclusion: Tinnitus, in patients having hyperlipidemia, can be successfully dealt with by treating hyperlipidemia with lipid lowering agent atorvastatin.

Key Words: *Tinnitus. Hyperlipidemias. Atorvastatin.*

INTRODUCTION

Tinnitus is defined as the perception of a phantom sound in the absence of an external auditory stimulus. One in 10 adult suffers from tinnitus and one in 100 feel severely handicapped due to its effects on the quality of life.[1] Tinnitus is a relatively common disease among adults of advancing ages, having a 10 years cumulative incidence of 12.7%. It is prevalent among 7 - 20% of the older population. Tinnitology is a new branch consisting of multidisciplinary team dedicated to diagnosing and treating tinnitus.[2]

Tinnitus can be studied by identifying the area of origin, less commonly the jaw or turbulent flow in a vessel near the inner ear. Mostly it is attributed to ischaemia of inner ear. A more practical way of classifying tinnitus is to group it by etiology i.e. tinnitus of otologic and neurological origin, thereby helping in identifying the cause.[3]

Various theories have been proposed to explain the mechanism of tinnitus. The hypothesis include changes in the temporal firing patterns of neuronal activity, cross innervations of eighth nerve fibers, temporal dysfunction of inner and outer hair cells and disturbance in potentials of eighth cranial nerve. Regardless of the initiation of tinnitus, the primary pathology is the damage to the cochlea and eighth cranial nerve due to vascular ischaemia, ageing, loud noise exposure, viral infections or ototoxic drugs.[4] Cochlear damage results in hearing loss which results in imbalance of excitatory and inhibitory mechanisms on various levels of auditory pathways. These neuroplastic alterations in the central auditory pathways result in generation of tinnitus.[5]

Inner ear is an end organ and the blood supply of stria vascularis and hair cells is highly susceptible to vascular events. Hyperlipidemia leads to deposition of lipids in end arteries, thereby causing narrowing, resulting in compromised blood supply causing chronic hypoxia that disturbs cochlear metabolism. This also affects adversely the capability of the antioxidant enzymes which may result in accumulation of free radicals. Hair cells of the cochlea are prone to damage due to diminished supply of oxygen as well as due to accumulation of free radicals which cause peroxidative damage of hair cells.[6]

Tinnitus due to hyperlipidemia in theory may benefit from anti-hyperlipidemics. Atorvastatin is a synthetic lipid lowering agent which inhibits 3-hydroxy-3-methylglutaryl coenzyme (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in cholesterol synthesis.[7]

This study was designed and carried out to identify individuals with tinnitus with raised serum cholesterol and to determine the effects of a lipid lowering agent (Atorvastatin) on tinnitus in these patients.

[1] *Department of ENT, Combined Military Hospital, Rawalpindi.*
[2] *Department of Pathology, Armed Forces Institute of Pathology, Rawalpindi.*

Correspondence: Maj. Zeeshan Ayub, House No. 284, Street 405, F-10/4, Rawalpindi.
E-mail: zeeshanent@yahoo.com

Received: December 13, 2012; Accepted: August 07, 2014.

METHODOLOGY

After approval of hospital ethical committee, all patients presenting to ENT OPD, CMH, Rawalpindi, with complaints of persistent tinnitus and sensorineural hearing loss of atleast one year duration, were evaluated by taking a detailed history including exposure to loud sounds, ototoxic drugs, intensity and temporal distribution of tinnitus. Individuals with history of ear trauma and tumours of auditory system were excluded from the study. A thorough ear, nose and throat examination was carried out. Sensorineural hearing loss was confirmed by performing tunning fork tests and counterchecked using pure tone audiometry. Serum cholesterol was measured by enzymatic method using Hitachi 912 analyzer. One hundred and five patients of tinnitus and sensorineural hearing loss with raised serum cholesterol were selected after consent. As 7 patients were lost to follow-up, the rest i.e. 98 patients of tinnitus and sensorineural hearing loss with raised serum cholesterol were included in the study.

All of the 98 patients underwent pre-therapy tinnitus scoring using the Tinnitus Handicap Questionnaire. All these patients were advised Tab Atorvastatin 40 mg once daily and low cholesterol diet (Table I). After 8 months interval, serum lipid profile was performed again and the patients were purposefully divided into two groups, “responsive” and “unresponsive” depending upon serum lipid control. Responsive group were taken as those individuals whose serum cholesterol after 8 months of therapy returned to within the normal limits (< 200 mg/dl), and those having no significant lowering in serum cholesterol level, were placed in unresponsive group.

Post-therapy tinnitus scores were reassessed using 'Tinnitus Handicap Questionnaire' in all the patients. Improvement in tinnitus score was considered if tinnitus score fell by 10 or more points on post therapy assessment. The data thus recorded was summarized as tinnitus being present pre therapy (before starting tablet atorvastatin) in all 98 patients, and tinnitus either being absent or present post therapy (after 8 months treatment with atorvastatin) in all the cases, both the groups were compared by Fisher's exact test and p-value less than 0.05 was considered as significant.

RESULTS

A total of 98 patients were included in the study. Pre-therapy (before starting tablet atorvastatin) serum cholesterol levels ranged from 239 - 356.

After 8 weeks treatment with atorvastatin, 51 patients (52%) fell into the responsive group (serum cholesterol < 200 mg/dl), while 47 (48%) fell into the unresponsive group (serum cholesterol > 200 mg/dl). Serum cholesterol levels in responsive group ranged from 156 - 197 mg/dl and in the unresponsive group ranged from 241 - 369 mg/dl. Post-therapy (i.e. after 8 months treatment with atorvastatin) in both responsive and unresponsive groups tinnitus scores were recorded using 'Tinnitus Handicap Questionnaire' and marked as tinnitus absent or present. Improvement in tinnitus score (marked as tinnitus absent) in the responsive group was seen in 36 (70.5%) patients, whereas 15 (29.4%) did not show any appreciable improvement (tinnitus present). In the unresponsive group, only 2 (4.22%) patients had improvement in tinnitus (tinnitus absent) post therapy and 45 (95.7%) had no improvement (tinnitus present). Improvement in tinnitus scores was compared in the responsive and unresponsive groups using Fisher's exact test and were found to be statistically significant (p < 0.001) as shown in Table II, thereby showing that lowering of serum cholesterol levels in patients suffering from tinnitus, helps in alleviating the symptom of tinnitus.

Table I: Low cholesterol diet.

Dietary modification for patients with hyperlipidemias.
Food or drink to be avoided
1. Bakery items (cakes, cookies etc.)
2. Red meat
3. Fried meat
4. Dried fruits or nuts
5. Butter, margerine
Food and drinks to be used sparingly
1. Mutton
2. Milk
3. White bread
4. Honey
Food and drinks that can be used
1. Chicken
2. Skimmed milk
3. Vegetables
4. Fruits

Table II: Post-therapy tinnitus improvement (n=98).

Group	Tinnitus improvement post therapy		p-value
	Yes	No	
Responsive group (n=51)	36 (70.5%)	15 (29.4%)	< 0.001*
Unresponsive group (n=47)	2 (4.2%)	45 (95.7%)	

** Significant p-value by using Fisher's exact test.*

DISCUSSION

The universal goal of all the research performed on tinnitus is to understand the physiological mechanisms of tinnitus, in order to develop pharmacological agents to treat this pathology. Tinnitus is not a single pathology but rather an amalgam of multiform system. The pathology leading to this multiform defect lies in the blood supply to the inner ear.[8] In hyperlipidemia, vascular factors are not the only pathology responsible for the auditory dysfunction. Lipid deposition (lipidosis) of the membranous inner ear has been documented by Norena *et al*. as an alternate mechanism. The authors have shown

that the lateral wall of outer hair cells in guinea pig cochlea incorporates water-soluble cholesterol as a foreign body. This uptake of cholesterol is accompanied by a foreign body reaction resulting in increased stiffness of the cells, leading to transduction abnormalities.[9]

In the inner ear, Fetoni *et al*. found that simvastatin protects the auditory function of mice that suffer from a deficiency in apolipoprotein E and were given a high fat diet.[10] However, they attributed this effect to control of hyperlipidemia. Syka *et al*. showed that atorvastatin slows down the age related deterioration of inner ear function in mice. They suggested that atorvastatin reduces endothelial inflammatory process and potentially thwarts off the deleterious effects of inflammation on the blood supply to the inner ear.[11]

Satar *et al*. found that hypercholesterolemia causes auditory dysfunction and transduction problem if dietary cholesterol is kept at a high level for a long-time. The high cholesterol usually affects stria vascularis and hair cells.[12]

In this study, 51 patients not only responded to atorvastatin in lowering the serum cholesterol levels, but also showed improvement in tinnitus scores, indicating the relationship between hyperlipidemia and tinnitus. Sutbas *et al*. in a prospective study on 120 patients also found that tinnitus and hearing loss co-existing with hyperlipidemias showed significant improvement when serum cholesterol levels returned to normal with antihyperlipidemics.[13] Tatsuhito *et al*. found a significant improvement in tinnitus scores of patients who were started on antihyperlipidemics.[14] Pulec *et al*. reported an 83% improvement in tinnitus among patients who were treated for hyperlipidemia.[15] Conversely Canis *et al*. found no improvement in tinnitus in patients of hyperlipidemias who were treated with simvastatin for 4 months.[16] Kojima demonstrated marked hearing improvement and tinnitus scores with antihyperlipidemics in a study on 12 patients of chronic hearing loss and tinnitus.[17] These results were also validated by Erdem *et al*. by showing presence of distortion product Otoacoustic Emission (OAE) in cases of hyperlipidemias.[18] Presence of distortion product Otoacoustic Emission signifies outer hair cell damage and their reversal with the use of lipid lower agents points towards a vascular ischaemic cause of tinnitus. Further evidence to this phenomenon is gained by studying the presence of distortion product Otoacoustic Emissions which though are not a pathognomonic sign of inner ear damage, but when present signify vascular damage to cochlea.[19]

The audiometric profile can be compared with tinnitus pitch matching to confirm otological origin of tinnitus. Further evidence to this phenomenon is gathered by studying the effect hearing aids have on the intensity of tinnitus by matching the pitch of the offending noise.[20]

Annexure 1: Tinnitus handicap questionnaire.

Instructions: The purpose of this questionnaire is to identify difficulties that you may be experiencing because of your tinnitus. Please answer every question. Please do not skip any questions.
Score: Yes 2, Sometimes 1, No 0
1. Because of your tinnitus, is it difficult for you to concentrate?
Yes / Sometimes / No
2. Does the loudness of your tinnitus make it difficult for you to hear people?
Yes / Sometimes / No
3. Does your tinnitus make you angry?
Yes / Sometimes / No
4. Does your tinnitus make you feel confused?
Yes / Sometimes / No
5. Because of your tinnitus, do you feel desperate?
Yes / Sometimes / No
6. Does tinnitus cause you minor accidents?
Yes / Sometimes / No
7. Because of your tinnitus, do you have trouble falling to sleep at night?
Yes / Sometimes / No
8. Is tinnitus limiting your ability to interact positively with your family?
Yes / Sometimes / No
9. Does your tinnitus interfere with your ability to enjoy your social activities?
Yes / Sometimes / No
10. Because of your tinnitus do you find that you are often irritable?
Yes / Sometimes / No
11. Does your tinnitus get worse when you are under stress?
Yes / Sometimes / No
12. Because of your tinnitus, do you often feel tired?
Yes / Sometimes / No
13. Because of your tinnitus, is it difficult for you to concentrate?
Yes / Sometimes / No
14. Because of your tinnitus, do you feel that you have a terrible disease?
Yes / Sometimes / No
15. Because of your tinnitus, do you feel depressed?
Yes / Sometimes / No
Total score: Pre-therapy: (Tinnitus present) Post therapy: (Tinnitus: present / absent)

Modified from Stanford University Tinnitus Handicap inventory[9]

CONCLUSION

Tinnitus, in the patients having hyperlipidemia, can be successfully dealt with by treating hyperlipidemia lipid lowering agents like atorvastatin, thereby providing a realistic approach to the management of such patients.

REFERENCES

1. Elgoyhen AB, Langguth B. Pharmacological approaches to the treatment of tinnitus. *Drud Discov Today* 2010; **15**:300-5.
2. Elgoyhen AB, Langguth B, Vanneste S, De Ridder D. Tinnitus: network pathophysiology-network pharmacology, *Front Syst Neurosci* 2012; **6**:1.
3. Nondahl DM, Cruickshanks KJ, Wiley TL, Klein BEK, Klein R, Chappell R, Tweed TS. The 10-year incidence of tinnitus among older adults. *Int J Audiol* 2010; **49**:580-85.
4. Schecklmann M, Vielsmeier V, Steffens T, Landgrebe M, Langguth B, Kleinjung T. Relationship between audiometric

slope and tinnitus pitch in tinnitus patients: insights into the mechanisms of tinnitus. *PLoS One* 2012; **7**:e34878.

5. De Ridder D, Elgoyhen AB, Romo R, Langguth B. Phantom percepts: tinnitus and pain as persisting aversive memory networks. *Proc Natl Acad Sci USA* 2011; **108**:8075-80.
6. Sezer ED, Sozmen EY, Nart D, Onat T. Effect of atorvastatin therapy on oxidant-antioxidant status and atherosclerotic plaque formation. *Vasc Health Risk Manag* 2011; **7**: 333-43.
7. 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**:244-50.
8. Guitton MJ. Tinnitus: pathology of synaptic plasticity at the cellular and system levels. *Front Syst Neurosci* 2012; **6**:12.
9. Norena AJ. An integrative model of tinnitus based on a central gain controlling neural sensitivity. *Neurosci Biobehav Rev* 2011; **35**:1089-109.
10. Fetoni AR, Piacentini R, Fiorita A, Paludetti G, Troiani D. Water-soluble coenzyme Q10 formulation (Q-ter) promotes outer hair cell survival in guinea pig model of Noise Induced Hearing Loss (NIHL). *Brain Res* 2009; **1257**:108-16.
11. Syka J, Ouda L, Nachtigal P, Solichova D, Semecky V. Atrovastin slows down the deterioration of inner ear function with age in mice. *Neurosci Lett* 2007; **411**:112-6.
12. Satar B, Ozkaptan Y, Surucu HS, Ozturk H. Ultrastructural effects of hypercholesterolemia on the cochlea. *Otol Neurotol* 2001; **22**:786-9.
13. Sutbas A, Yetiser S, Satar B, Akcam T, Karahatay S, Saglam K. Low-cholesterol diet and antilipid therapy in managing tinnitus and hearing loss in patients with noise-induced hearing loss and hyperlipidemia. *Int Tinnitus J* 2007; **13**:143-9.
14. Tatsuhito O, Masaharu U, Yutaka N. A study of tinnitus vertigo patients with hyperlipidemia. *Otologia Fukuoka* 2002; **48**:313-8.
15. Pulec JL, Pulec MB, Mendoza I. Progressive sensorineural hearing loss, subjective tinnitus and vertigo caused by elevated blood lipids. *Ear Nose Throat J* 1997; **76**:716-20.
16. Canis M, Olzowy B, Welz C, Suckfüll M, Stelter K. Simvastatin and Ginkgo biloba in the treatment of subacute tinnitus: a retrospective study of 94 patients. *Am J Otolaryngol Head Neck Med Surg* 2011; **32**:19-23.
17. Kojima Y, Ito S, Furuya N. Hearing improvement after therapy for hyperlipidemia in patients with chronic-phase sudden deafness. *Ann Otol Rhinol Laryngol* 2001; **110**:105-8,
18. Erdem T, Ozturan O, Miman MC, Ozturk C, Karatas E. Exploration of the early auditory effects of hyperlipoproteinemia and diabetes mellitus using otoacoustic emissions. *Eur Arch Otorhinolaryngol* 2003; **260**:62-6.
19. Kaltenbach JA. Tinnitus: models and mechanisms. *Hear Res* 2011; **276**:52-60.
20. Sereda M, Hall DA, Bosnyak DJ, Edmondson-Jones M, Roberts LE. Re-examining the relationship between audiometric profile and tinnitus pitch. *Int J Audiol* 2011; **50**: 303-12.