Effect of Lowered Bone Mineral Density on the Outcomes of Audiological Tests: A Preliminary Study

Aditi Gargeshwari, Niraj Kumar Singh, Prawin Kumar, Raghav Hira Jha

Department of Audiology, All India Institute of Speech and Hearing, Mysore, Karnataka, India

Abstract

Introduction: Calcium ions are important for efficient release of neurotransmitters during the transduction process in cochlea. It also plays a pivotal role in recycling of potassium ions. A deficiency in optimal functioning of calcium, which is seen in osteopenia and osteoporosis, could therefore hinder the recycling of K+ ions and cause dysfunction in the neurotransmitter release and thereby sensorineural hearing loss. The deficiency in the bone mineral density (BMD) can also result in microfractures in the middle ear bones and thereby affect its transmission properties. However, few studies have investigated the audiological findings in osteoporosis and none in osteopenia. Therefore, the present study aimed at assessing the effect of lowered BMD on the outcomes of the audiological tests. **Method:** The study incorporated 11 participants with osteoporosis, 12 with osteopenia, and 12 having normal BMD. All the participants underwent detailed structured case history, pure-tone audiometry, speech audiometry, immittance evaluation, and distortion-product otoacoustic emission (DPOAE). **Results:** There was a trend toward increase in pure-tone average and speech recognition threshold (SRT) and reduction in speech identification scores in the two clinical groups than the controls; however, this was significant only for SRT ($P < 0.05$). The osteoporosis group revealed significantly higher proportions of ears with absent acoustic reflexes and DPOAEs than control group and osteopenia group. **Conclusion:** The findings point to the detrimental impact of reduction in BMD on the entire auditory periphery. Therefore, the audiological evaluation should consist of tests capable of evaluating the auditory system functioning at different levels when evaluating persons with osteopenia or osteoporosis.

Keywords: Audiological evaluations, bone mineral density, osteopenia, osteoporosis

Introduction

Bones are living tissues that constitute the skeletal mass of the human body. By a process called bone remodeling, the bone gets added or subtracted by 5%–10% every year.[1] Bone remodeling involves two processes: the creation of new bone cells by the osteoblasts and the absorption of the old bone cells by the osteoclasts.[2] However, when the bone absorption occurs at a higher rate than the bone production, the bone volume remains unchanged but the bone gaps become larger and the bone density decreases.[3] The decreased bone mineral density (BMD) affects the skeletal system of the body and increases the risk of fractures.[4]

The decrease in the density of the bone is generally presented in terms of the "T-" scores. Normally functioning individuals have a T-score of 0.[5] If the T-scores are 1–2.5 standard deviations below the normal mean scores, they are classified as osteopenia, and if the scores are below 2.5 standard deviations of the T-scores obtained in normal, it is termed as osteoporosis.[5] Thus, decreased BMD can classify the individuals as having osteopenia (−1.1≤ T-score ≤−2.5) or osteoporosis (T-scores of −2.6 onward in the negativity).[5]

Osteoporosis is a disease characterized by low bone mass and microarchitectural deterioration in the bone tissues, leading to enhanced bone fragility and a consequent increase in the fracture risk.[6] Osteoporosis is a disorder in which calcium and phosphates hydroxyapatite [$Ca_{10}(PO_4)_6(OH)_2$] levels are reduced.[7] There also occur changes in the potassium, manganese, and calcium levels in this disorder.[5-7] Osteoporosis can occur in all populations and at all ages. Although more prevalent in postmenopausal females, it often

Access this article online

Quick Response Code:

Website: www.jisha.org

DOI: 10.4103/jisha.JISHA_4_17

Address for correspondence: Raghav Hira Jha, Department of Audiology, All India Institute of Speech and Hearing, Manasagangothri, Mysore - 570 006, Karnataka, India. E-mail: raghav.jha415@gmail.com

How to cite this article: Gargeshwari A, Singh NK, Kumar P, Jha RH. Effect of lowered bone mineral density on the outcomes of audiological tests: A preliminary study. J Indian Speech Language Hearing Assoc 2017;31:29-35.

goes unrecognized in other populations. Osteoporosis is a devastating disorder with significant physical, psychosocial, and financial consequences.[7] Osteopenia is also a medical condition which is also characterized by similar BMD reduction but of lesser severity than osteoporosis.

Ear is a structure composed of connective tissues in the form of bones and cartilages. The external ear consists of pinna and external auditory canal which are cartilaginous in structure. The middle ear is a conductive system composed of ossicular chain, namely, the malleus, incus, and stapes.[8] The inner ear is housed in the petrous portion of the temporal lobe.[9] Decrease in the BMD is known to affect the skeletal system of the ear, thereby resulting in hearing loss of various kinds. Absorption of bones in the middle ear causes thinning of them, which results in changes of the middle ear characteristics.[10] Changes can also occur due to stiffness changes in the soft-tissue elements of the middle ear,[11] epitympanic spurs, and proliferation of fibrous tissue adjacent to the ossicles.[12]

The process of bone demineralization, which causes osteopenia and osteoporosis, can also affect the temporal bone in which the cochlea is housed.[13] It can result in mechanisms which can cause sensorineural hearing loss. It can also result in compression of the auditory nerve,[14] obstruction of vascular shunts,[15] and narrowing of the auditory canal.[14] It has been seen that as the bone fragility increases, the hearing loss (degree and prevalence) increases.[13] In cases with osteopenia and osteoporosis, changes in bone density, mass, and dampening of the finely tuned motion mechanics of the middle ear cause conductive hearing loss whereas changes occurring in the otic capsule and the temporal bone affect the inner ear causing sensorineural hearing loss.[15,16] Furthermore, calcium ions are important for the efficient release of the neurotransmitters during the transduction process in the cochlea.[17,18] They (calcium ions) also play a vital role in the recycling of potassium ions, especially removal of K^+ ions from the hair cells.[19,20] A deficiency in calcium, which is seen in osteopenia and osteoporosis, could therefore hinder the recycling of K^+ ions and cause dysfunction in the neurotransmitter release and thereby sensorineural hearing loss. However, there are very few studies that have explored the audiological test findings in osteoporosis and none in osteopenia.

The previous studies have shown higher prevalence of hearing loss[21-23] and 1.76 times higher prevalence of sudden sensorineural hearing loss[24] in individuals with osteoporosis than those with normal BMDs. However, these studies have looked into only one aspects of audiological testing and not reported the findings of various audiological tests in the same set of individuals. Therefore, the present study was conducted with the aim to assess the effect of lowered BMD (osteopenia and osteoporosis) on the outcomes of the audiological tests.

Objectives

1. To find the effect of decreased BMD on pure-tone audiometry and speech audiometry
2. To find the effect of reduced BMD on immittance evaluation outcomes
3. To find the effect of reduced BMD on otoacoustic evaluation outcomes
4. To study the relationship between reduced mineral density and the outcomes of various audiological evaluations.

Methods

Participants

The study incorporated 35 participants who underwent BMD testing as part of a camp for identification of osteopenia and osteoporosis. Based on the classification recommended by the World Health Organization for BMD,[5] 11 individuals identified as having osteoporosis (mean age = 62 years, standard deviation = 8.8), 12 as having osteopenia (mean age = 62.4 years, standard deviation = 9.6), and 12 as having normal BMD (mean age = 58 years, standard deviation = 10.5) served as participants in the present study. There was no significant difference in age between the groups ($P > 0.05$, multivariate analysis of variance [ANOVA]). All participants had either normal hearing sensitivity or sensorineural hearing loss. Participants with conductive hearing loss caused by middle effusions or perforations of the tympanic membrane were not included in the study. Further, none of the participants selected in the study had any history or complaints of diabetes mellitus, noise exposure, or intake of any ototoxic medication. Furthermore, all but two participants had normal blood pressure. The two participants with a history of hypertension had normal BMD, and their blood pressure readings of the past 2 months preceding the evaluations used in the present study were well within the normative range. All the participants underwent detailed structured case history which was followed by pure-tone audiometry, speech audiometry, immittance evaluation, and distortion-product otoacoustic emission (DPOAE).

Instrumentation and test environment

A calibrated two-channel clinical audiometer Inventis Piano with TDH-39 headphones housed in MX-41/AR ear cushions was used for finding air-conduction thresholds and doing speech audiometry. Radio ear B-71 bone vibrator along with the same audiometer was used for measuring bone conduction thresholds. A calibrated middle ear analyzer Grason-Stadler Incorporated Tympstar was used for obtaining tympanogram type, static compliance, ear canal volume, acoustic reflex threshold, and middle ear resonance frequency. The Otodynamics ILO V6 was used for recording DPOAEs. All the tests were carried out in acoustically treated air-conditioned rooms with permissible noise level as per the guidelines recommended by the American National Standards Institute.[25]

Procedure

All participants were comfortably seated in a chair. Pure-tone thresholds were obtained across octave frequencies from 250 to 8000 Hz for air conduction and 250–4000 Hz for bone conduction. Pure-tone average (PTA) was calculated as the

mean of 500 Hz, 1000 Hz, 2000 Hz, and 4000 Hz. PTA of more than 15 dB was considered as an indication of hearing loss.[26] Speech recognition thresholds (SRTs) were obtained through live presentation of standardized spondee word lists in Kannada.[27] Speech identification scores (SISs) were obtained at 40 dBHL above the SRT using phonetically balanced word lists.[28]

Tympanometry was done using 226 Hz probe tone to assess the normal functioning of the middle ear, where the tympanometric peak pressure, static compliance, and the ear canal volumes were noted down. The pump speed during the tympanometry was varied at the rate of 50 daPa/s. Multifrequency tympanometry was carried out to obtain the middle ear resonant frequency. Ipsilateral and contralateral acoustic reflex thresholds were obtained at 500 Hz, 1000 Hz, 2000 Hz, and 4000 Hz.

DPOAEs were recorded using two tones with the ratios of their frequency being 1.2 (f2/f1 = 1.2) and the level of lower frequency (L1) being 65 dBSPL and that of the higher frequency (L2) being 55 dBSPL. Responses were obtained at 1 kHz, 1.5 kHz, 2 kHz, 3 kHz, 4 kHz, and 6 kHz. DPOAEs were considered to be present at any frequency if emissions were at least 6 dBSPL >2 standard deviations above the mean noise floor.[29]

Statistical analyses

One-way repeated measures ANOVA was done for ears with group on the between-subject factor for PTA, speech recognition threshold, SISs, static compliance, and resonance frequency. Chi-square test was done to find association between groups and PTA, groups and SRT, groups and SIS, groups and static compliance, groups and resonance frequency, and groups and acoustic reflex thresholds at 500 Hz, 1000 Hz, 2000 Hz, and 4000 Hz. The equality of test for proportions was done to find the differences if any in the response rates of acoustic reflex and DPOAEs.

Results

The outcomes of audiometry

The audiometric procedures included pure-tone audiometry and speech audiometry (SRT and SIS). Pure tone thresholds were obtained across all the octave frequencies from 250 Hz to 8000 Hz in both the ears for all the individuals in each of the groups. Figure 1 shows mean and 95% confidence intervals of air-conduction pure-tone thresholds from the individuals in these three groups.

The group of individuals with osteoporosis had the highest (worst/poorest) thresholds whereas the controls with normal BMD levels had the lowest (best) thresholds. The SRT and SIS findings reflected a similar trend to the PTA with poorest SRTs and lowest SIS values observed for osteoporosis and best SRTs and highest SIS values found in the control group with normal BMD scores. Table 1 shows outcome of descriptive statistics for air-conduction pure-tone thresholds,

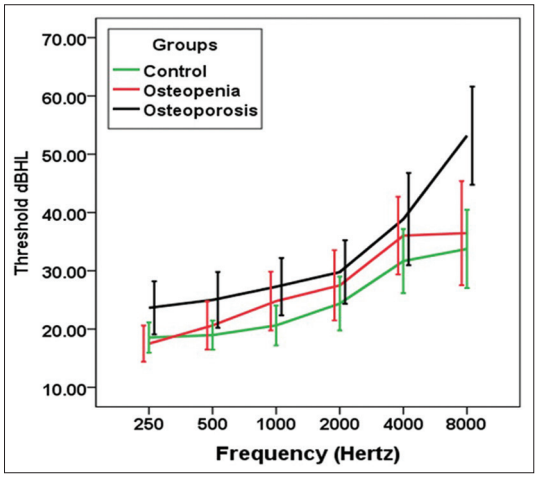

Figure 1: Mean and 95% confidence intervals of air-conduction pure-tone thresholds across frequencies (left panel) for all the subjects in the three groups

bone conduction thresholds, speech reception thresholds, and speech (word) identification scores in each group.

To examine the statistical significance of the above-mentioned observations, one-way repeated measures ANOVA was done for ears with group as the between-subject factor. The results revealed no significant main effect of ear (F[1] = 0.680, P = 0.416) and group (F[2] = 3.47, P = 0.43) on the PTA thresholds. Likewise, there was no significant main effect of ear (F[1] = 0.03, P = 0.95) and group (F[2] = 1.05, P = 0.36) on SRT. The results of SIS also reflected a similar pattern of no significant main effect of ear (F[1] = 0.67, P = 0.97) and group (F[2] = 0.68, P = 0.52) on SIS.

An increasing trend was noted for the mean PTA and SRT and a decreasing trend for mean SIS from control to osteopenia to osteoporosis group. The Chi-squared analyses revealed no significant association between groups and their PTA. However, there was a significant association between groups and SRT (χ^2[2] = 35.7, P = 0.000) and also between groups and SIS (χ^2[2] = 131.85, P = 0.000).

The outcomes of immittance evaluation

The immittance evaluation included tympanometry and reflexometry. The resonance frequencies were also obtained from both ears of all the participants, irrespective of the group. Table 2 shows the outcome of descriptive statistics for parameters assessed using immittance evaluation.

The results of one-way repeated measures ANOVA for ears with group as the between-subject factor was done and the results showed no significant main effect of ear (F[1] = 0.35, P = 0.55) or group (F[2] = 0.02, P = 0.97) on static compliance. In the similar vein, there was no significant main effect of ear (F[1] = 0.25 P = 0.62) and group (F[2] = 59, P = 0.56) on ear canal volume and also of ear (F[1] = 0.03, P = 0.87) and group (F(2) = 2.39, P = 0.11) on resonance frequency. However, there was a significant association between static compliance and groups (χ^2[2] = 43.14, P = 0.001) and also

Table 1: Mean, median, and standard deviation of pure-tone average thresholds, speech recognition thresholds, and speech identification scores of the control, osteopenia, and osteoporosis groups

	Control group			Osteopenia			Osteoporosis		
	Mean	Median	SD	Mean	Median	SD	Mean	Median	SD
PTA	24.11	23.75	8.32	27.23	25.00	11.98	30.68	30.00	12.04
BC	18.20	19.75	7.37	19.02	19.75	11.4	22.84	24.75	10.45
SRT	23.54	27.50	8.65	27.08	25.00	11.50	29.77	30.00	12.95
SIS	95.33	100.00	6.74	93.33	96.00	9.33	91.63	100.00	9.79

PTA: Four frequency (500 Hz, 1000 Hz, 2000 Hz, and 3000 Hz) pure-tone average; SRT: Speech reception threshold; SIS: Speech (word) identification scores; SD: Standard deviation; BC: Average of bone conduction thresholds at 500 Hz, 1 kHz, 2 kHz, and 4 kHz

Table 2: Mean, median, and standard deviation of static compliance, ear canal volume, and resonance frequency of the middle ear across the three groups

	Control group			Osteopenia			Osteoporosis		
	Mean	Median	SD	Mean	Median	SD	Mean	Median	SD
SC	0.88	0.65	0.70	0.75	0.80	0.40	0.95	0.80	0.51
ECV	1.53	1.50	0.27	1.34	1.20	0.30	1.41	1.50	0.38
RF	779.16	750.00	118.8	857.23	850.00	171.3	783.33	800	203.60

SC: Static compliance measured in mmho; ECV: Ear canal volume measured in ml; RF: Resonance frequency measured in Hz; SD: Standard deviation

between resonance frequency and groups ($\chi^2[2] = 46.49$, $P = 0.00$) with more individuals with higher values for static compliance and lower values for resonance frequencies in two clinical groups than the control group.

In terms of the acoustic reflexes, both ipsilateral and contralateral acoustic reflexes were absent in more number of individuals at each frequency in the two clinical groups than the control group. The absence of acoustic reflex at all the four frequencies was considered an abnormal result. The osteoporosis group had nearly 32% of individuals with absence of reflexes whereas the osteopenia group and control group had 0.83% and 0.41% individuals with absent reflexes, respectively. The equality of test for proportions revealed that significantly higher proportion of individuals in osteoporosis group had absence of acoustic reflexes than the osteopenia group ($Z = 2.47$, $P = 0.01$) and the control group ($Z = 2.00$, $P = 0.04$). There was no significant difference between the osteopenia group and the control group ($Z = 0.59$, $P = 0.55$). Figure 2 shows the response rate of ipsilateral and contralateral acoustic reflexes and the outcome of equality of test for proportions for comparison of response rates between the groups.

The outcomes of distortion-product otoacoustic emission

DPOAEs were obtained across frequencies. DPOAEs were considered to be absent whenever the signal-to-noise ratio (SNR) was below 6 dB SNR or the amplitude was <−5 dB. Nearly 63% of the control ears had the presence of DPOAE at least at one frequency as against 38% and 37% in the osteopenia and the osteoporosis group, respectively. The equality of test for proportions was administered for between-group comparisons for response rates in DPOAEs. The result revealed absence of responses in significantly higher proportion of individuals in osteopenia ($Z = 1.73$, $P = 0.08$) and osteoporosis ($Z = 1.77$, $P = 0.07$) than the control group. There was no significant difference in OAE response rate between osteopenia and osteoporosis.

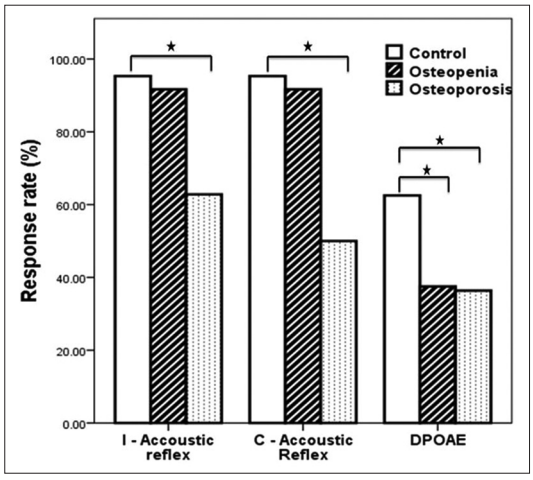

Figure 2: Percentage of participants in each group that had presence of acoustic reflexes and distortion product otoacoustic emissions. Star marked pairs were significantly different from each other

Discussion

In the present study, although there was no significant difference in the proportion of individuals having hearing loss between the groups, the osteoporosis group had higher prevalence of hearing loss than the control group (90.9% vs. 75%). The finding of higher prevalence of hearing loss in osteoporosis group than the control group is in agreement with the previous reports.[21-24] This might be attributed to alteration in the metabolism of Ca^{2+} ions, which is the main essence of these pathologies. Ca^{2+} ions are present in the hair cells as well as in the neurons and are helpful in the release of the

neurotransmitters at the synapses between the hair cells and neurons and also at the synapses between the neurons.[30] They (Ca^{2+}) also help in maintaining the stiffness of tip links in the stereocilia necessary for mechanical transduction and also in recycling of the neurotransmitters and the potassium ions from the cells.[31] Therefore, Ca^{2+} ions help not only in transduction of longitudinal sound waves but also in propelling the electrical impulses along the entire auditory pathway from cochlea to the auditory cortex.

Reduction in BMD affects the homeostasis of the calcium and alters its level in the cochlea. Studies have shown hypercalcemia in serum of individuals with reduced mineral density.[32,33] This is because of decreased intestinal absorption of calcium.[34] Since calcium is vital to many systems' functioning in the body, lack of intestinal calcium absorption causes the body to start using the calcium in the bones. Hence, when the bone resorption occurs at a faster rate compared to absorption, the calcium levels are increased in the serum, also known as hypercalcemia. However, there is no clear understanding about the relationship between calcium level in the blood and that in the endolymph or intracellular calcium concentration.

If the calcium levels in the endolymph are high because of its increased level in blood, it will result in blocking of microphonic potentials and consequently affect hair-cell transduction.[35] Long-lasting elevated levels of calcium are known to activate the calcium-dependent phosphatase calcineurin which in turn is known to trigger apoptosis (self-programmed cells death).[36] Elevated calcium levels trigger calpain activation in hair cells which in turn limits proteolysis, thereby triggering protein destruction process which ultimately would lead to cell death. This could result in hearing loss in a high proportion of individuals suffering from osteoporosis. Some investigators have put forth another explanation regarding the pathophysiology of elevated calcium-dependent hearing loss. Increased amount of calcium ions binds to the intracellular site of mechanotransduction channels or a closely associated subunit, which causes closure of the channel itself within a few milliseconds.[31,37] This acts like a fast adaptation which elevates the threshold. However, the above description is based on the assumption that increased serum calcium levels also result in its increased levels in the endolymph and intracellular calcium in the hair cells. However, this (hypercalcemia of endolymph and hair cells cytoplasm) has not yet been proven experimentally in case of osteoporosis.

There might be a possibility therefore that calcium levels are reduced further in the endolymph and hair cells. In case of reduction in Ca^{2+} ions, the stiffness of the tip links might be affected which would alter its spring-like properties, thereby affecting regulation of potassium and smooth transmission of the electrical impulses. Thus, either increase or decrease in the levels of calcium secondary to altered bone remodeling can affect the functioning of the cochlea adversely, thereby causing hearing loss in more number of individuals with osteopenia and osteoporosis and result in higher thresholds in these individuals than individuals with normal levels of Ca^{2+} ions (control group). A trend toward this effect was observed in the present study.

Although there are no previous reports of immittance evaluations in osteopenia and osteoporosis, the pathology in these cases (which is reduced calcium levels) can cause a significant change in the middle ear functioning owing to the middle ear being a bone-dominated structure. This is precisely shown by the findings of significant association between groups and static compliance at tympanic membrane and also between groups and resonance frequency. A previous study has reported thinning of the ossicles in cats with low calcium levels,[10] which could be correlated to a reduction in stiffness by virtue of applying lesser pressure on tympanic membrane. Since the resonance frequency is directly proportional to the stiffness and inversely proportional to the mass in a second order mechanical system such as our middle ear,[38] the reduction in stiffness consequent to reduction in BMD would result in decrease in resonance frequency of middle ear. Further, the patients with reduced BMD are reported to be susceptible to microfractures of the ear ossicles[39] which can go undetected but can result in reduced resonant frequency of the middle ear. The presence of microfractures within the ossicular chain in some of the participants with reduced BMD in the present study might have contributed to the significant association between the above-mentioned variables. However, this is an assumption based on the results. It could be confirmed through high-resolution computerized tomography scans, which however were not taken up in the present study. Future studies could do with inclusion of such investigation.

The results of the present study showed a significant association between group and ARTs (higher ART values in osteoporosis and lower in control group as evidenced by mean and median values). This could be related to the altered levels of calcium in the endolymph. Studies have shown that calcium ions are important for the optimal cochlear functioning and release of neurotransmitters,[18] as described above. An increase/reduction in calcium levels above/below the optimum would result in apoptosis or reduced generation of evoked potentials. The stapedial reflex is triggered only when there is built-up of sufficiently large action potential at the facial motor neuron.[40] Therefore, triggering of acoustic reflex will necessitate higher amount of neurotransmitter release in order for the sufficiently large action potential to reach the motor neurons of the facial nerve so that a stapedial reflex could be generated. Either hair-cell damage due to increased calcium levels or reduced action potential due to reduction of calcium might be the reason behind higher ARTs in individuals with osteopenia and osteoporosis than the controls.

The DPOAEs in the present study were completely absent in a significantly higher proportion of the clinical groups than the control group. The absence of OAEs in individuals with reduced BMD may be either due to increased calcium levels causing damage to the outer hair cell which are the

source of otoacoustic emissions or due to reduced utility of calcium ions as calcium has been shown to be vital for the recycling of potassium ions outside of the hair cell.[41] A higher concentration of potassium within the cell at the time of stimulation would result in lesser exchange of potassium ions and therefore lesser change in the potential difference between the fluids across the membrane of an outer hair cell. This potential difference is vital for the electromotility action of the outer hair cell which in turn is important for generation of the otoacoustic emissions.[18,42] Reduction in the BMD is likely to cause alteration in the metabolism at the level of the cochlea and hence result in reduced electromotility and thereby reduced or absent DPOAEs in a higher proportion of individuals in the clinical groups than the control groups.

Increased absorption of the bones due to increased osteoclast cells results in release of excess calcium from the bones in the body fluid. It is seen that there occurs higher levels of calcium in the blood, urine, and saliva in persons with osteoporosis and osteopenia. However, to the best of our knowledge, there has not been any study reporting calcium levels in the inner ear fluid in these individuals. Increased level of calcium in the inner ear fluid fastens the process of hair-cell death and reduced levels will affect recycling of potassium and neurotransmitter release. Thus, either increased or decreased alteration in the levels of calcium secondary to reduced BMD can cause alteration in the functioning of cochlea and consequently result in altered outcomes on the audiological tests.

Conclusions

The results of the present study reflected higher degree of hearing loss, higher ARTs, more compliance of tympanic membrane, and more abnormality in DPOAEs in the clinical groups than the control group. This shows that there is detrimental impact of reduction in BMD on the entire auditory periphery. Therefore, while evaluating persons with osteopenia or osteoporosis, the audiological evaluation should consist of tests capable of evaluating the auditory system functioning at different levels.

Acknowledgments

We would like to thank the Director and HOD Audiology, All India Institute of Speech and Hearing for permitting to carry out the research and providing the necessary infrastructure.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Duan Y, Turner CH, Kim BT, Seeman E. Sexual dimorphism in vertebral fragility is more the result of gender differences in age-related bone gain than bone loss. J Bone Miner Res 2001;16:2267-75.
2. Clarke B. Normal bone anatomy and physiology. Clin J Am Soc Nephrol 2008;3 Suppl 3:S131-9.
3. Wang TC, Lin CC, Lin CD, Chung HK, Wang CY, Tsai MH, *et al.* Increased acquired cholesteatoma risk in patients with osteoporosis: A retrospective cohort study. PLoS One 2015;10:e0132447.
4. Randell KM, Honkanen RJ, Kröger H, Saarikoski S. Does hormone-replacement therapy prevent fractures in early postmenopausal women? J Bone Miner Res 2002;17:528-33.
5. World Health Organization, WHO Scientific Committee on the Assessment of Osteoporosis at Primary Health Care Level. Summary Meeting Report; 1-17 May, 2004.
6. Osteoporosis prevention, diagnosis, and therapy. NIH Consens Statement 2000;17:1-45.
7. Vibert D, Sans A, Kompis M, Travo C, Muhlbauer RC, Tschudi I, *et al.* Ultrastructural changes in otoconia of osteoporotic rats. Audiol Neurootol 2008;13:293-301.
8. Kringlebotn M. Network model for the human middle ear. Scand Audiol 1988;17:75-85.
9. Lewis ER, Leverenz EL, Bialek WS, editors. The Vertebrate Inner Ear. CRC Press LLC; 1985.
10. Kanzaki S, Ito M, Takada Y, Ogawa K, Matsuo K. Resorption of auditory ossicles and hearing loss in mice lacking osteoprotegerin. Bone 2006;39:414-9.
11. Nager GT. Cholesteatoma of the Middle Ear: Pathogenesis and Surgical Indication. In: Cholesteatoma, First International Conference; 1977. p. 193-203.
12. Davies DG. Malleus fixation. J Laryngol Otol 1968;82:331-51.
13. Monsell EM. The mechanism of hearing loss in Paget's disease of bone. Laryngoscope 2004;114:598-606.
14. Applebaum EL, Clemis JD. Temporal bone histopathology of Paget's disease with sensorineural hearing loss and narrowing of the internal auditory canal. Laryngoscope 1977;87(10 Pt 1):1753-9.
15. Nager GT. Paget's disease of the temporal bone. Ann Otol Rhinol Laryngol 1975;84(4 Pt 3 Suppl 22):1-32.
16. Khetarpal U, Schuknecht HF. In search of pathologic correlates for hearing loss and vertigo in Paget's disease. A clinical and histopathologic study of 26 temporal bones. Ann Otol Rhinol Laryngol Suppl 1990;145:1-16.
17. Vergara C, Latorre R, Marrion NV, Adelman JP. Calcium-activated potassium channels. Curr Opin Neurobiol 1998;8:321-9.
18. Hacohen N, Assad JA, Smith WJ, Corey DP. Regulation of tension on hair-cell transduction channels: Displacement and calcium dependence. J Neurosci 1989;9:3988-97.
19. Chan DK, Hudspeth AJ. Ca2+ current-driven nonlinear amplification by the mammalian cochlea *in vitro*. Nat Neurosci 2005;8:149-55.
20. Eatock RA, Corey DP, Hudspeth AJ. Adaptation of mechanoelectrical transduction in hair cells of the bullfrog's sacculus. J Neurosci 1987;7:2821-36.
21. Ozkiris M, Karaçavus S, Kapusuz Z, Balbaloglu O, Saydam L. Does bone mineral density have an effect on hearing loss in postmenopausal patients? Ann Otol Rhinol Laryngol 2013;122:648-52.
22. Kahveci OK, Demirdal US, Yücedag F, Cerci U. Patients with osteoporosis have higher incidence of sensorineural hearing loss. Clin Otolaryngol 2014;39:145-9.
23. Weng SF, Chen YS, Liu TC, Hsu CJ, Tseng FY. Prognostic factors of sudden sensorineural hearing loss in diabetic patients. Diabetes Care 2004;27:2560-1.
24. Yeh MC, Weng SF, Shen YC, Chou CW, Yang CY, Wang JJ, *et al.* Increased risk of sudden sensorineural hearing loss in patients with osteoporosis: A population-based, propensity score-matched, longitudinal follow-up study. J Clin Endocrinol Metab 2015;100:2413-9.
25. American National Standards Institute. Maximum Permissible Ambient Noise Levels for Audiometric Test Rooms. (ANSI S3.1-1991). New York: ANSI; 1991.
26. Clark JG. Uses and abuses of hearing loss classification. ASHA 1981;23:493-500.
27. Rajashekar B. The Development and Standardization of an SRT Test for Adults and Children in Kannada. Unpublished Master's Dissertation. University of Mysore; 1976.
28. Vijayalakshmi CS, Yathiraj A. Phonemically Balanced Wordlist in Kannada. Developed in Department of Audiology, All India Institute of Speech and Hearing, University of Mysore; 2005.

29. Starr A, Picton TW, Sininger Y, Hood LJ, Berlin CI. Auditory neuropathy. Brain 1996;119(Pt 3):741-53.
30. Glowatzki E, Fuchs PA. Transmitter release at the hair cell ribbon synapse. Nat Neurosci 2002;5:147-54.
31. Cheung EL, Corey DP. Ca2+ changes the force sensitivity of the hair-cell transduction channel. Biophys J 2006;90:124-39.
32. Saha MK, Agrawal P, Saha SG, Vishwanathan V, Pathak V, Saiprasad SV, *et al.* Evaluation of correlation between salivary calcium, alkaline phosphatase and osteoporosis - A prospective, comparative and observational study. J Clin Diagn Res 2017;11:ZC63-6.
33. Lee SB, Lee CH, Kim YJ, Kim HM. Biochemical markers of bone turnover in benign paroxysmal positional vertigo. PLoS One 2017;12:e0176011.
34. Gallagher JC, Riggs BL, Eisman J, Hamstra A, Arnaud SB, DeLuca HF. Intestinal calcium absorption and serum Vitamin D metabolites in normal subjects and osteoporotic patients: Effect of age and dietary calcium. J Clin Invest 1979;64:729-36.
35. Tanaka Y, Asanuma A, Yanagisawa K. Potentials of outer hair cells and their membrane properties in cationic environments. Hear Res 1980;2:431-8.
36. Rivera A, Maxwell SA. The p53-induced gene-6 (proline oxidase) mediates apoptosis through a calcineurin-dependent pathway. J Biol Chem 2005;280:29346-54.
37. Ricci AJ, Kennedy HJ, Crawford AC, Fettiplace R. The transduction channel filter in auditory hair cells. J Neurosci 2005;25:7831-9.
38. Van Camp KJ, Vanhuyse VJ, Creten WL, Vanpeperstraete PM. Impedance and admittance tympanometry. II. Mathematical approach. Audiology 1978;17:108-19.
39. Swinnen FK, De Leenheer EM, Goemaere S, Cremers CW, Coucke PJ, Dhooge IJ. Association between bone mineral density and hearing loss in osteogenesis imperfecta. Laryngoscope 2012;122:401-8.
40. Borg E. On the neuronal organization of the acoustic middle ear reflex. A physiological and anatomical study. Brain Res 1973;49:101-23.
41. Jagger DJ, Ashmore JF. Regulation of ionic currents by protein kinase A and intracellular calcium in outer hair cells isolated from the guinea-pig cochlea. Pflugers Arch 1999;437:409-16.
42. Brownell WE. Outer hair cell electromotility and otoacoustic emissions. Ear Hear 1990;11:82-92.