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ORIGINAL ARTICLE

Association of Vitamin D Deficiency in Patients with Tinnitus with Normal Audiogram

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Abstract

In the present study we aim to evaluate serum vitamin D levels in participants having tinnitus with normal audiometric findings. Total 98 participants in the age range 20–70 year were included in the study. Participants underwent detail case history, ear examination, pure tone audiometry and impedance audiometry. 68 participants with subjective tinnitus for more than 3 months and with normal audiometric thresholds and "A" type tympanogram were included in study group and 30 participants without tinnitus in the control group. The participants fullfillng the inclusion criteria underwent thorough tinnitus evaluation which included administration of tinnitus severity index tinnitus handicap inventory, psychophysical evaluation of tinnitus (pitch matching, loudness matching) and assessment of Vitamin D levels. It was seen that the mean Vitamin D levels were significantly lower in study group, and out of 68 participants only 11 had optimal Vitamin D levels, 57 (83%) had Vitamin D levels less that 30 mg/dl. In the control group 20 (66%) had vitamin D deficiency. The difference came out to be statistically significant. Our study suggests that there is a link between vitamin D and tinnitus, in view of these findings we recommend evaluating serum Vitamin D levels in patients of chronic idiopathic tinnitus, especially in adults with normal hearing. Our study suggests vitamin D deficiency may be one of the risk factor for tinnitus in people with normal hearing in the absence of other manifestations.

Keywords Vitamin D · Tinnitus · Pure tone Audiogram

Introduction

Tinnitus is a phantom auditory perception of sound without any corresponding acoustic or mechanical correlate in the cochlea. It is one of the most common hearing disturbance affecting 17% of general population and 33% of Elderly.[1]. It is present in 1 out of 5 older adults, and every 1 out of 10 with tinnitus experience severe tinnitus that is interfering with daily life [2].No such statistics is available on Indian population. Pathogenesis of tinnitus is complex and multi factorial. Traditionally it has been known to be of otologic etiology but advances in neuroimaging techniques have shifted towards its neurological origin.The pathophysiology of subjective tinnitus is theorized to involve disturbances at the level of cochlear hair cells, neural and central auditory pathway .It is generally accepted that hearing loss is one of the leading risk factors associated with tinnitus. Disturbances in central auditory pathway may develop after cochlear injury or hearing loss resulting in auditory equivalent of phantom limb pain [3].

Vitamins and micronutrients are known to play a significant role in human metabolism.Litrature on association of nutrition and hearing delineates increased incidence of hearing loss by lack of micronutrients such as vitamin A, B, C, D and E, zinc, Mg, Se, iron and iodine [4–6]. We can find various studies in the literature on the hearing loss and vitamin deficiencies. Gerald B Brooks noted that vitamin D deficiency is a common place in patients with otosclerosis causing impairment of cochlear structure and deafness[7]. Prevalence of vitamin D deficiency in patients with sudden sensorineural hearing loss was more than healthy people. Evidences show the role of vitamin D in inner ear disease is related to calcium metabolism, demineralization of the cochlea, cochlear sensitivity to chronic ischemic effects, and lysosomal enzymes imbalance leading to degeneration of auditory structures [8].

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The role of vitamins and minerals in relation to tinnitus has not been examined extensively despite biological plausibility. Recent researchers have found vitamin D receptors on calcium channel transport system of cochlea and are known to act to regulate proper calcium balance in addition it had known to play role in adequate mylinization and neurotransmission of nerves [9].These findings elucidate the possibility of its role in maintaining proper auditory function and possible role in triggering /eggagerating tinnitus. We could only find limited number of studies linking serum vit D with presence or absence of tinnitus. Its deficiency has been linked to many problems which are known to coexist with tinnitus such as dementia, depression, diabetes mellitus, autism, and schizophrenia[10] .Few studies have also shown association to factors that deeply contribute to origin of tinnitus [11],Meniere"s disease [12] BPPV [13] old age deafness.[14].

The result from a recent metanalysis done show that serum vitamin D levels are frequently decreased (by around 22 according to our estimation) in patients with tinnitus compared to patients without tinnitus thus pointing out at the role of vitamin D levels in development and exaggeration of tinnitus [15].P Dawas et al. administered questionnaire to adults to garner information on their nutritional status.In this study in final regression models highest vitamin D intake was associated with low odds of tinnitus while low quintile of vitamin D intake was associated with high hearing difficulties and tinnitus .[6].

Vitamin D deficiency prevails in epidemic proportions all over the Indian subcontinent, with a prevalence of 70–100% in the general population[16] [10].The incidence of vitamin D Deficiency is extremely common in Ear Nose Throat disease (E.N.T.) patients [14].We assume that high prevalence of tinnitus and vitamin D deficiency may have an association .Determining preventive factors and risk factors of tinnitus may be helpful to improve clinical awareness and treatment of the tinnitus. Though Hearing loss is regarded as a trigger for neuroplastic changes giving rise to the tinnitus percept but tinnitus has also been known to occur without hearing loss.8% of patients with tinnitus are known to have pure tone audiometric thresholds within the normal range [18]. The prevalence of tinnitus with a normal audiogram was thought to indicate that tinnitus could be present without any cochlear damage. However, recent findings have suggested that substantial damage to the auditory periphery can occur without affecting audiometric thresholds[19]To our knowledge no study has been done to explore the relationship of vitamin D deficiency and tinnitus in normal hearing adults. Regardless of many efforts and research,pathophysiology of tinnitus without hearing loss remains poorly understood. The variable risk factors and heterogeneity in presentation has lead to difficulty in management of the same especially in cases without hearing loss.

Thus in the present study we aim to evaluate serum vitamin D levels in patients having tinnitus with normal audiometric findings. We aim to determine association of vitamin D deficiency in patients with tinnitus and normal audiogram with our null hypothesis that there is no association of prevalence of tinnitus in subjects with vitamin D deficiency with normal audiogram. The threefold objectives of the study were (1) To determine the prevalence of Vitamin D deficiency in patients having subjective tinnitus for more that 3 months with normal audiogram as compared to subjects without tinnitus. (2) To Compare vitamin D levels of younger adults and older adults with tinnitus. (3) To descriptively evaluate the characteristic of tinnitus in patients having Vitamin D deficiency.

Material and Methods

Study Design It was a prospective analytical case controlled study conducted in department in MMMC&H Hospital,Solan,India.

Study Participants and Procedure

The study protocol was reviewed and approved by the institutional ethical committee. All the participants with tinnitus reporting to otolaryngology department from to April 2020 to October 2020 were evaluated for inclusion in the study based on certain inclusion and exclusion criteria. Attendants of the patients who agreed to participate in the study were evaluated to be included in control group. The sample size was not statistically determined but was based on the cases available.After applying appropriate eligibility criteria, total 100 participants were evaluated to be included in study. Two participants did not report back after Vitamin D evaluation. Therefore the final group was composed of 68 participants in the study group and 30 in control group. Consent was taken from all the participants.

Detailed history was taken of all the participants followed by ear examination under microscope, pure tone audiometry, and impedance audiometry.Detailed tinnitus evaluation was done for the participants in the study group which included administration of tinnitus questionnaire (Tinnitus severity Index and Tinnitus Handicap inventory) and psycoacoustic tinnitus evaluation.All the participants were then sent for serum Vitamin D assessment.

Inclusion Criteria

Study group included participants in age range of 20 to 70 year, normal audiometric thresholds "A" type tympanogram and having subjective tinnitus for more than 3 months .Both unilateral as well as bilateral tinnitus were included in the study.

Control group included healthy subject without tinnitus matching in age and sex with normal audiometric thresholds and "A" type tympanogram.

Exclusion Criteria

Participants with history of hearing loss,otitis media, middle ear effusion, otitis external, ear surgery pulsatile, head trauma, intermittent, occasional tinnitus or any ear related disease, neurological disorder, toxic exposure, hypertension, diabetes or musculoskeletal disorders and subjects on Vitamin D Supplimentation were excluded from the study group .

In control group in addition to above, patients having tinnitus were also excluded.

Audiological Evaluation Audiological Testing Pure tone Audiometry was performed in a sound treated room with a double channel audiometer.(Interacoustics model AC40) with standard headphones (TDH-49) calibrated to ISO 9001 Standards.Pure-tone air conduction hearing thresholds were taken at conventional frequenciesat 250 Hz,500 Hz, 1 K,2 K,4 K,8 K,.Bone conduction threshold were determined at 250 Hz,500 Hz, 1 K,2 K,4 K.Subjects having three frequency pure tone average of 500 Hz, 1 K,2 K less than 25dBHL in both ears were considered normal hearing. Impedance audiometry was done with Intraacoustic AT235 impendence Audiometer.

Tinnitus Evaluation The tinnitus severity and disability was measured based on the the administration of tinnitus handicap inventory (THI) and Tinnitus severity index (TSI).

On TSI patients were assessed on sixty points. Patients who scored 1-12 points were classified as very mild, 13 – 24 as mild, 25 –36 as moderate 37– 48 as severe 49 –60 as catastrophic.

On THI, patients were assessed on 25 questions. Patients who received 0- 16 were classified as having no handicap,18 – 36 as mild handicap, 38– 56 as moderate handicap ,58– 76 as severe handicap and 78 – 100 as catastrophic handicap.

In addition to THI and TSI two additional questions were asked regarding the history of noise exposure and difficulty hearing in noise.Patients were requires to report in "Yes" or "No".

Psycoacoustic tinnitus evaluations was done using the same equipment that was used for pure tone audiometry. In addition a HDA 200 Ear Phone was used for assessment of high frequency tinnitus.The tinnitus analyses consisted of tinnitus pitch matching ,tinnitus loudness matching determining the maximum loudness levels.

Pitch of tinnitus: pitch matching was done by two alternate forced choice method. The level was initially set at 5 db above the measured audiometric level. The patient was required to choose the closest match to the pitch of tinnitus.

Loudness matching was done by ascending method. The level was adjusted in two dB steps until the patient indicated that the tone matched the loudness of their tinnitus repeated 3 times [20].

Tinnitus loudness level was calculated as the intensity level of tinnitus minus baseline hearing thresholds of tinnitus noise.

Patients were sent for lab testing to assess Vitamin D 25(OH)d3 level. It was classified as optimal if serum Vitamin D levels ≥ 30 ng/ml and low if Vitamin D levels were < 30 ng/ml.

The data was analyzed using IBMSPSS 23.Continuous variables were presented as means and SD. Descriptive analysis was done. Chi square test was used to compare qualitative and t- test for quantitative data of the demographic characteristic. The vitamin D levels among the control and study were compared using two tailed t-test.p value < 0.001 was taken to indicate statistical significance.

Results

The study group included 68 participants (age range 20 to 70 years and mean age 42.11 ± 15.09) with tinnitus. The control group included 30 subject (age range 22 to 58 years with mean 45 .8 ± 18.09) without tinnitus. The KS (Kolmogorov - Smirnov) test was used to examine the normal distribution of the data set. Table 1 shows demographics of the participants.

Table 1 Demographics of the participants

	Study group n (68)	Control group n(30)
AGE (mean SD)	42.11 ± 15.09	45 0.8 ± 18.09
20 to 50years(n)	40	14
51 to 70years(n)	28	1
Gender		
Male	40	15
female	28	15

It was seen that the prevalence of Vitamin D deficiency in patients having subjective tinnitus for more that 3 months with normal audiogram was high as compared to prevalence of Vitamin D deficiency in subjects without tinnitus. The mean Vitamin D levels were significantly lower in study

Table 2 Distribution of Vitamin D levels in study Group and control group

	Study Group	Control Group	Sig
Vitamin D Levels (ng/ml)	15.23	33.51	
Optimal n(percentage)	11	20(66%)	0.10
Low n (percentage)	57(83%)	10(33%)	< 0.001

Table 3 Comparison of vitamin D levels of younger adults and older adults with tinnitus

	Young Adults	Old Adults	Sig
N	40	28	
Optimal n(%)	4(10%)	11(39%)	< 0.001
Insufficient n(%)	36(90%)	17(60%)	< 0.001

Table 4 Comparisons of mean of Characteristics of tinnitus in patients with optimal Vitamin D levels and with Vitamin D ≥ 30ng/ml

Characteristic	Subjects with Vitamin D ≤ 30ng/ml	Subjects with Vitamin levels ≥ 30 ng/ml	
N	53	15	
Age (mean SD)	49	37	
Duration (mean SD)	4.7	4.82	
Bil(%)	62%	22%	< 0.001
Unilateral(%)	38%	78%	< 0.001
Tinnitus Loudness (mean SD)	35	40	
Tinnitus Pitch(mean SD)	3137 Hz	2930 Hz	
TSI Score(mean SD)	69	29	< 0.001
THI Score(mean SD)	72	30	< 0.001
Noise Exposure(%)	62%	42%	
Difficulty Hearing In Noise (%)	40%	26%	< 0.001

group. Out of 68 subjects only 11 had optimal Vitamin D levels ,57 (83%) participants had Vitamin D levels less that 30 ng/ml. In the control group 20 (66%) had vitamin D defeciency. The difference came out to be statistically significant with p value < 0.001.Thus refuting our null hypothesis Table 2 shows the distribution of Vitamin D levels in study Group and control group.

Table 3. shows comparison of vitamin D levels of younger adults and older adults with tinnitus. It is seen that 90% of young adults with tinnitus and normal audiogram had Vitamin D deficiency as compared to 60% older adults .

Descriptive analysis of the characteristic of tinnitus in patients having Vitamin D deficiency showed 62% of subjects with Vitamin D deficiency had bilateral tinnitus which was significantly higher that the group with optimal Vitamin D. Comparisons of mean of Characteristics of tinnitus in patients with optimal Vitamin D levels and with Vitamin D ≤ 30ng/ml is shown in Table 4.

THI and TSI Scores were also seen to be significantly higher in subjects with Vitamin D deficiency. The analysis of two additional questions was also done on subjects all the

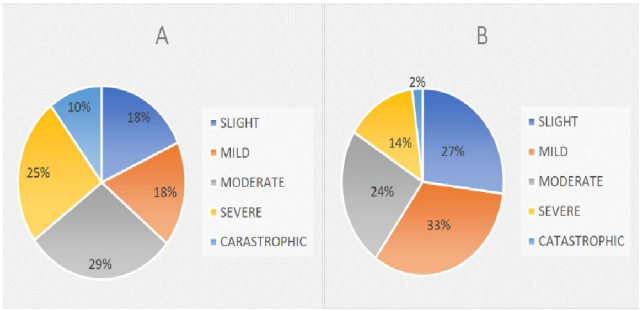

Fig. 1 (A) Distribution of THI scores in subjects with vitamin D levels < 3Ong/ml. (B) Distribution of THI scores in subjects with Vitamin D Levels > 30

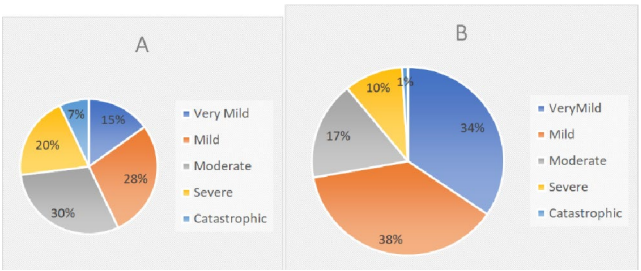

Fig. 2 (A) Distribution of TSI scores in subjects with vitamin D levels < 3Ong/m1. (B) Distribution of TSI scores in subjects with Vitarnin D Levels > 30ng/ml

participants. Higher number of participants with vitamin D deficiency had difficulty in speech understanding in noisy places. It was also observed that maximum participants with vitamin D deficiency scored in moderate and severe range on THI. In contrast none of the participants with optimal vitamin D levels scored in catastrophic range and maximum participants scored in slight and mild range as shown in Fig. 1. Similar distribution was seen on TSI as shown in Fig. 2.

Discussion

Our study reported high prevalence of Vit D deficiency in patients having subjective tinnitus as compared to the group without tinnitus. Though it is seen that even in the general population Vitamin D deficiency prevails in epidemic proportions the results from recent meta analysis reveal that vit D levels are frequently decreased (by around 22%) in patients with tinnitus as compared to without tinnitus which is in accordance with our study.

Restricted literature could be found linking serum vitamin D in presence and absence of tinnitus. As of now we could only come across two studies investigating the influence of vitamin D and tinnitus. Nowaczewska M et al 2021 displayed high prevalence of

vitamin D deficiency in patients with tinnitus and its effect on tinnitus parameters, but their study included subjects with great number of co morbidities which could coexist with tinnitus and with vitamin D deficiency. Most of these were not included in our study as we explored on subjects without hearing loss [20]. Elsayeed S MA 2021 assessed the potency of Vitamin D supplementation on severity of tinnitus in normal hearing subjects. They reported significant reduction in tinnitus severity in cases of idiopathic tinnitus[21].

The exact mechanism by which Vitamin D influence tinnitus needs to be elusidated. Vid D deficiency is associated with SNHL possibly by interfering with Ca metabolism leading to demineralization of cochlea, and microcirculation in cochlea [8].Vit D is also known to have direct effect on otoconia through control and regulation of Ca absorption and uptake and ion channel expression. Evedience exist that vid D may cause an erosive TMJ (temporomendibular joint) arthritis by stimulating production of inflammatory cytokinesis [20] which may further cause tinnitus. As inflammatory mechanism are known to play role not only in hearing loss but also in tinnitus, hence anti inflammatory role of vit D may play role in tinnitus[21].Altered cytokine production may be responsible for exacerbating the pathophysiological changes of otitis media in patients deficient in Vit D [22].Vit D is also known to play role in defence mechanisum of body as it regulate the level of CYP27B1 enzyme which is responsible for secretion of major antimicrobial catheliciedin. Weak immune system may lead to frequent attacks of URI And otitis media[23].

In the present study subjects taken were without history of any hearing loss or recurrent otitis media. Only two subjects had history of TMJ disorder but they had normal vitamin D levels others had no comorbid conditions and were otherwise healthy.Few other mechanisums through which Vid D could affect tinnitus are proposed. Studies have shown high prevelance of headaches in tinnitus. There are evidences that idiopathic headaches, pain and tinnitus have overlaping pathophysiological mechanisums and may influence each other by sharing specific alterations in thalamocortical activity. There is reciprocal involvements of both auditory and associative/paralimbic areas leading to generation of tinnitus[24].Fibromyalgia is a common pain condition associated with tinnitus,propable common pathophysiological mechanism of tinnitus and fibromyalgia show high incidence of tinnitus and Vit D defeciency in fibromyalgia.The association between chronic pain and tinnitus emphasizes the importance of examining comorbid pain in tinnitus patients [26, 27]. Mg plays a role as a main cofactor for vitamin D production and activated vitamin D enhance intestinal absorption of Mg therefore it is proposed that restricted Mg absorption may lead to tinnitus exerbation[21][14].

It is widely agreed that neuroplastic changes in the central auditory system, give rise to the tinnitus percept, and one of the mechanisms by which this occurs is a decrease in inhibitory neurotransmission.Vitamin D has been reported to modulate the biosynthesis of nero transmitters and neurotrophic factors [10].Outer hair cell damage is known to trigger plastic readjustments in DCN(Dorsal cochlear nucleus) leading to hyperactivity in DCN.Auditory plasticity theory of tinnitus proposes that damage to the cochlea enhances nural activity in central auditory pathway,auditory plasticity emerges as a consequence of aberrant pathway and tinnitis might be auditory system's analog to phantom limb sensation in amputees [27]. Developmental vitamin D deficiency may leads to these brain changes. Vitamin D diminish the production of nitric oxide by inhibiting the expression of nitric oxide syntheses .Nitric oxide regulates neorotransmission and vasodialatation. Nitric oxide is involved in plastic neural changes associated with tinnitus and may contribute to tinnitus generation,Vitamin D deficiency by increasing nitric oxide production and further endothelial dysfunction (which in turn induces a dysfunction of microceuculation in inner ear) may generate tinnitus, inhibition of zinc induced oxidative stress may also act as effective antioxident to prevent tinnitus [20].Thus the role of vitamin D in cognitive, neuroprotective function and neuro transmitters presents a compelling rationale for association of vitamin D with generation of tinnitus especially in patients with normal audiograms.

Secondly it was seen that the significantly higher number of younger adults with tinnitus had Vit D deficiency as compared to the older adults with tinnitus.These findings are similar to the findings of Nowaczewska et al. 2021 but contrary to the accepted observation that Vit D photosynthesis markedly declines with age[30]. Few studies show that the prevalence of vitamin D deficiency decrease with age and that younger adults and males shown higher prevalence of vitamin D deficiency while few other studies report the opposite showing inconsistent results with respect to age and gender [31]. Several factors contribute to production of vitamin D in body e.g. strength of UV rays, duration of sun exposure, geographical area, season ,place of residence, ,pigmentation in skin ,dietry factors e.t.c. Studies have also indicated impact of sesonal changes and geographical region

over vit D deficiency. The geographic regions at higher latitudes result in greater vitamin D deficiency even with higher daily intake of vitamin D and low serum d in winters month compared with summer has been shown[32].Our study was done on patients residing at high altitude of approx 1550 above sea level in summer season. No prevalence study could be found pertaining to this geographical region in adult population. Though we could find few studies done on children of this region indicating high prevalence of Vit D deficiency[33].Our findings could be attributed to the lifestyle differences between young and elderly. Especially in urban areas young adults are office workers and do not have time for physical exercise in day time which affects their sun exposure. By contrast older adults are retired and have more time for outdoor physical activities. It was seen that vit D deficiency did not significantly affects the psycoacoustic of tinnitus though more patients with Vit D defeciency had high tinnitus severity index and High tinnitus handicap as compared to subjects with optimal vitamin D levels. Vit D deficiency may possibly aggravate, anxiety, depression and may influence reaction tinnitus .

The analysis of the characteristic of tinnitus in patients having Vitamin D deficiency showed higher scores on TSI and THI in subjects with low Vit D levels as compared to subjects with optimal vitamin D indication that subjects with Vitamin D defeciency and tinnitus were more bothered by their tinnitus as compared to subjects with optimal vitamin D and tinnitus. No significant difference was seen in psycoacoustic measures of pitch and loudness of the two groups .It is also shown in few other studies that the psycoacoustic measures of tinnitus are not correlated to the THI TSI scores as they do not assess the reaction and the social impact of the tinnitus[34].It is also seen that tinnitus severity scores are closely related to psychological conditions of stress and depression in tinnitus patients [35].On the other hand, vitamin D levels are significantly associated with the risk of anxiety symptoms and depression [36].Thus, it is possible that vitamin D deficiency by aggravating anxiety and depressive symptoms may influence reactions to tinnitus. Significantely high number of subjects with vitamin D defeciancy had bilateral tinnitus as compared to subjects with optimal vitamin D levels.We included subjects with both unilateral and bilateral tinnitus as we wanted to see the overall prevelence of tinnitus in subjects with vitamin D defeciency and secondly we assume that the disturbances caused due to Vit D defeciencies may initially involve only one ear and later may or may not involve the other ear, in addition as we had only included subjects with normal hearing thesholds, ear specific factors causing tinnitus were not expected .

It was also seen the patients with tinnitus and normal audiogram show difficulties in perception of speech in noisy environment. As also reported in present study that more subjects reported difficulty in understanding speech in noise inspite of normal audiometric thresholds in subjects with vitamin D defeciency as compared to the subjects with optimal vitamin D levels. Studies show normal hearing thresholds can also be accompanied by impaired function of efferent fibers that project from the brainstem to the cochlea[35]. These subtle auditory damage may be more clearly revealed in more sensitive audiological tests as OAEs,acoustic reflexes ABR e.t.c. Further studies should be done to study the impact of vitamin D deficiency on these tests and also to objectively determine the level of difficulty in speech perception in noise in patients with Vitamin D deficiency through speech in noise tests and effect of the Vit D supplimentation on these tests.

Despite of our efforts, this study has limitations. The sample size was not statistically determined but was based on the cases available the study was conducted during Covid period with restricted case load. Moreover conceptual developments in research has shown that in medical research even small sample size can be used as biases are easy to control especially with restricted case load. Anderson and vingrys has shown that small samples may be enough to show presence of an effect but not for estimating effect size [36].The detail information about patients/controls lifestyle, workplace, sun exposure history of pains, headaches and, physical activity diet, headache was not included all of which might influence the vitamin D status and tinnitus.

Our study suggests that there is a link between vitamin D and tinnitus, in view of these findings we recommend evaluating serum Vitamin D levels in patients of chronic idiopathic tinnitus, especially in adults with normal hearing. Our study suggests vitamin D deficiency may be the main tinnitus risk factor in people with normal hearing in the absence of other manifestations. In view of the significant prevalence of vitamin D deficiency

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Declarations

Conflict of interest There are no conflict of intersest.

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