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RESEARCH ARTICLE

Estimation of outer hair cells function in chronic bilateral tinnitus patients with normal hearing using distortion product otoacoustic emissions

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Abstract

Background and Aim: It is not clear if the measurement of distortion product otoacoustic emissions (DPOAE) at frequencies above 8 kHz adds any value in determining the differences in the cochlear function between patients with and without tinnitus. This study aimed to compare DPOAE in the frequency range of 0.5−10 kHz in patients with normal hearing with and without tinnitus.

Methods: This comparative cross-sectional study was conducted on 20 individuals with tinnitus and normal hearing as a study group (SG) and a control group (CG) of 20 normal-hearing individuals without tinnitus. The DPOAE was measured with F_1/F_2 = 1.22 and intensities of F_1 = 65 dB SPL and F_2 =55 dB SPL in the frequency range of 0.5−10 kHz, moreover in the frequency of tinnitus in SG and corresponding frequency in CG.

Results: DPOAE level at 10 kHz did not differ significantly between SG and CG (p = 0.491). However, the mean of overall DPOAE level, DPOAE level at the frequency of tinnitus, and F_2 values of 2.5, 5, and 6.298 kHz were significantly lower in SG than CG (p < 0.05).

Conclusion: Measurement of DPOAE at 10 kHz did not seem to add any value in determining the differences in the cochlear function between patients with and without tinnitus. However, decreased DPOAE levels at 2.5, 5, and 6.298 kHz which were observed among patients who have tinnitus and normal hearing, indicates some outer hair cells damage that was not detectable by conventional audiometry.

Keywords: Tinnitus; normal hearing; outer hair cell; distortion product otoacoustic emission

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Introduction

Tinnitus is usually accompanied by hearing loss, but according to various reports, 8 to 10% of people with tinnitus have normal hearing [1]. The pathophysiological mechanism of tinnitus remains unknown, as the origin of tinnitus may be anywhere on the auditory pathways from the outer ear to the auditory cortex [2]. The source of tinnitus in people with normal hearing is

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much more ambiguous than in people with hearing loss [1]. According to a study by Weisz et al., normal hearing thresholds at the frequency range of 250−8000 Hz does not always show damage to the peripheral auditory system; in other words, lack of hearing loss at the frequency range of 250−8000 Hz does not rule out cochlear damage [3]. Some researchers suggested that there have been degrees of inner hair cell (IHC), auditory nerve [4], and outer hair cell (OHC) [5] damages that conventional audiometry has not been able to detect these damages. Furthermore, up to 30% of OHCs may be damaged before any hearing loss appears on the audiogram [6]. Evidence suggests that subtle changes in cochlear function can be detected by the otoacoustic emission (OAE) test even before significant changes in the patient audiogram occur [7]. Damage to cochlear OHCs is believed to be one of the main mechanisms of tinnitus. If human cochlear OHC is involved in tinnitus, the OAE test can be a reliable tool for recording OHC [8]. Measurement of distortion product otoacoustic emission (DPOAE) is the main type of OAE that evaluates the mechanical activity of OHC in patients with tinnitus [9]. In addition, due to the evaluation of the larger frequency spectrum, it is possible to examine the cochlear function from the basal (high frequencies) to the apical (low frequencies) [10]. There are several studies on DPOAE in people with tinnitus and normal hearing that have been performed in different ways such as pass/refer rates [11], normal/abnormal rates [12], DPOAE alteration [13,14], the slope of input/output function [15] and DPOAE amplitude in the frequency range of 1−8 kHz [16,17]. Past studies have reported significant differences in DPOAE parameters between patients with and without tinnitus when adjusted for their hearing thresholds up to 8 kHz [3,5,10]. However, it is not clear if the measurement of DPOAE at frequencies above 8 kHz adds any value in determining the differences in the cochlear function between patients with and without tinnitus. This is an important question because if there is a significant difference at 10 kHz then measuring DPOAEs at this frequency can be useful in this population. This study aimed to examine DPOAE in the frequency range of 0.5−10 kHz with three points per octave to the estimation of OHCs function in subjective, constant, chronic, and bilaterally tinnitus patients with normal hearing.

Methods

The study was conducted between December 2019 and September 2020 at the audiology clinic of Tehran University of Medical Sciences (TUMS). Approval was obtained from the TUMS Ethics Committee. The sample was selected by convenience sampling. A convenience sample is a type of non-probability sampling method where the sample is taken from a group of people easy to contact or to reach, therefore in this study; participants were selected among audiology clinic of TUMS, hospital audiology departments and private audiology clinics in Tehran. A written consent form was taken from all participants. This comparative cross-sectional study conducted on 20 subjects (12 men and 8 women) with tinnitus and normal hearing were nominated in the study group (SG), the control group (CG) comprised of 20 subjects (12 men and 8 women) without tinnitus and with normal hearing. Due to the lack of statistical information to estimate the sample size, the mean and standard deviation of DPOAE amplitude in a similar study were used to obtain the sample size [18]. The two groups had similar gender and age distribution. Common criteria for inclusion were age between 18 to 40 years, normal otoscopy, tympanometry type A, and hearing thresholds averaged across frequencies of 250, 500, 1000, 2000, 3000, 4000, 6000, and 8000 Hz, not more than 25 dB HL. The mean hearing threshold of audiometry at the frequency range of 250−8000 Hz is shown in Table 1. As age-related high-frequency hearing loss increases significantly after the fourth decade of life [19], in the present study subjects under the age of 40 were selected to eliminate the effects of age on normal hearing. Tinnitus in SG was subjective, bilateral, non-pulsatile, constant, and chronic (six months or more). Medical history for including the study were not having medicine usage for

Table 1. Mean hearing threshold (dB HL) in the frequencies of audiometry in study group and control group

	Mean (SD) hearing threshold (dB HL)							
Group	**250 Hz**	**500 Hz**	**1000 Hz**	**2000 Hz**	**3000 Hz**	**4000 Hz**	**6000 Hz**	**8000 Hz**
Study	−3 (2.37)	−3.12 (1.37)	−0.5 (2.87)	1.62 (2.03)	4.37 (2.67)	4.62 (2.33)	6.25 (2.5)	6.5 (2.35)
Control	−3.37 (2.18)	−3.37 (1.46)	−0.87 (2.72)	1 (2.05)	3.5 (2.35)	4.12 (2.03)	5.12 (2.74)	5.5 (2.23)
p	0.607	0.582	0.675	0.339	0.279	0.474	0.184	0.176

tinnitus during the past six months, history of otologic disorders, vascular disease, middle ear disease, vestibular disorders, head trauma, and neurological diseases; recent intake of ototoxic drugs such as salicylates, nonsteroidal anti-inflammatory drugs, aminoglycosides, diuretics; and chemotherapy/radiotherapy. Exclusion criteria were fatigue, ambient noise, and lack of cooperation of the subject to continue the tests. 47 participants enrolled in this study, but only 40 participants met the inclusion criteria. Of 7 individuals who were excluded from the study, one had age above 40 years old, one had existence of pulsatile tinnitus, one had an existence of tympanogram type C, one had tinnitus duration below six months, one had an existence of mild hearing loss at 6−8 kHz, one had an existence of mild to moderate notch at 4 kHz, and finally one had an existence of ear impacted because of cerumen. All participants underwent the following assessments: medical history taking, otoscopy examination, conventional pure-tone audiometry, tympanometry, tinnitus pitch-matching procedure, tinnitus loudness matching procedure, and DPOAE test. Prior performing the tests, audiometer calibrated in dB SPL, according to International Electrotechnical Commission (IEC) and American National Standards Institute (ANSI) audiometer standard. Also, DPOAE was calibrated based on actual stimulation frequencies and levels that will be used in the test, and stimulus values were corrected according to the IEC 60318-4 ear stimulator standard. Participants were first examined with an otoscope, and then performed conventional pure-tone audiometry using the modified Hoghson-Westlak ascending-descending method [20], tympanometry (frequency 226 Hz), tinnitus pitch-matching, and tinnitus loudness-matching based on Vernon and Meikle's procedures [21] inside the acoustic soundproofing chamber. In this evaluation, we asked the participant to compare the pitch created by noise or pure tone to the most noticeable pitch of tinnitus, then adjusted the intensity of noise or tone so that it had the similar loudness as their tinnitus. Next, DPOAE (using the Madsen Capella^2) was assessed by evoking two tones at a lower (F_1) and higher frequency (F_2), with the F_2/F_1 ratio = 1.22 (65 dB SPL for F_1 and 55 dB SPL for F_2) [22]. The following parameters were considered for all frequencies tested: signal-to-noise ratio ≥ 6 dB; the amplitude of the signal in the 90th percentile of the normal distribution for the frequencies tested [23,24]; frequencies of three points per octave from 0.5 to 10 kHz were considered [22]. Moreover, we evaluated the frequency of tinnitus in SG and corresponding frequency in CG according to the parameters mentioned above. Eventually, a comparison was made between right and left ears and SG in contrast with CG in these tests.

Statistical analysis of descriptive data was presented as mean and standard deviation (SD). Estimation of a normal distribution was elicited with the Kolmogorov–Smirnov test. The DPOAE level at frequencies of 498, 1250, 2500, 4000 Hz and overall DPOAE level had a normal distribution and frequencies of 625, 800, 996, 1602, 2002, 3154, 5000, 6298, 7998, 10000 Hz and frequency of tinnitus did not have a normal distribution. Parametric independent and paired

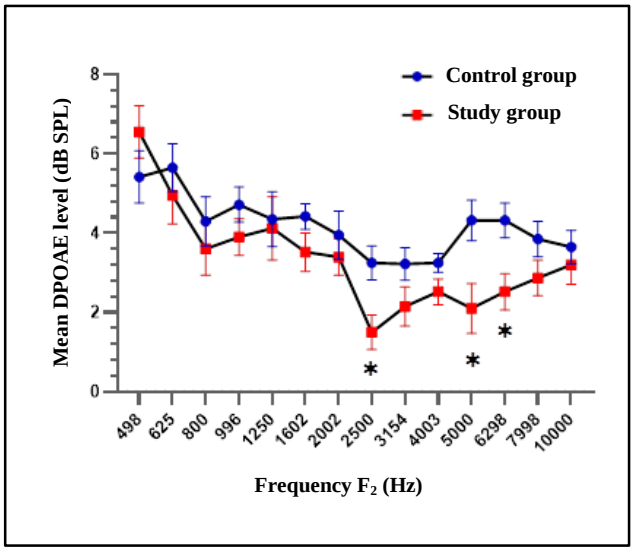

Fig. 1. Mean distortion product otoacoustic emission levels (in dB SPL) vs. F_2 frequency (in Hz). Squares: the study group; circles: the control group. Error bars indicate the standard errors. An asterisk indicates a significant difference between the mean values for the two groups.

t-tests were used for features with a normal distribution, and non-parametric Mann–Whitney U and Wilcoxon tests for features without normal distribution. Because of performing multiple comparisons, chances of obtaining a false positive result increase. The Bonferroni adjustment was used to minimize this problem, by changing the significance threshold, alpha. Therefore, the Bonferroni-adjusted level of 0.05 was considered as a significant level. all statistical analyses were performed using the SPSS version 22 for windows program (SPSS, Inc, an IBM Company, Chicago, Illinois, USA), G power version 3.1, and GraphPad Prism software version 9 (GraphPad Software, San Diego, CA) for figure plotting.

Results

The mean age of both SG and CG was 25.01 (SD = 4.01) years (range: 18−40 years). Age and gender were completely matched between SG and CG. The mean overall hearing threshold in the frequency range of 250−8000 Hz was 2.9 (SD = 1.42) and 1.45 (SD = 1.1) dB HL in SG and CG respectively. Results of pure-tone audiometry approved normal hearing in all participants, and there were no significant differences in the mean threshold levels between the groups (p = 0.12). The mean pitch and loudness of tinnitus in SG were 6400 (SD = 1046) and 4.5 (SD = 1.82) respectively. The frequency of tinnitus was 4000 Hz in one subject, 6000 Hz in 14 subjects, and 8000 Hz in 5 subjects. Comparison of DPOAE levels between right and left ears in both groups were not a significant difference at all frequencies tested (p > 0.05), so we used the mean of DPOAE levels at both ears for comparison between groups. The DPOAE test results at all frequencies are shown in Fig. 1. Our results showed mean DPOAE levels in SG were lower than CG for F_2 values from 625 to 10000 Hz, but only values of 2500, 5000 and 6298 Hz were lower significantly (2500 Hz; p = 0.007, CI = (0.75-2.74), 5000 Hz; p = 0.009, CI = (0.87-3.56), 6298 Hz; p = 0.007, CI = (0.52-3.07)). The mean DPOAE level at a frequency of 10 kHz in SG and CG was 3.2 (SD = 2.19) and 3.65 (SD = 1.88) respectively. There was no significant difference between the two groups in this frequency (p = 0.491). The mean of overall DPOAE levels in SG and CG were 3.35 (SD = 0.75) and 4.19 (SD = 0.75) respectively. There were significant differences in the mean of overall DPOAE levels between groups (p = 0.001; CI = 0.36-1.32). Furthermore, we have compared the DPOAE levels between ears and groups in the frequency of tinnitus, which we obtained via the pitch-matching test for each participant (Table 2). Comparison of DPOAE level between right and left ears in the frequency of tinnitus and corresponding frequency were not a significant difference (p = 0.23), but the mean of overall DPOAE levels in the frequency of tinnitus were significantly lower in SG than the corresponding frequency in CG (p = 0.013, CI = (0.37-2.97)).

Discussion

Tinnitus is a symptom that may be caused by different otological disorders. Despite recent advances in this field, the pathophysiology of

Table 2. Mean distortion product otoacoustic emission level (dB SPL) in the frequency of tinnitus in study group and corresponding frequency in control group

	Mean (SD) DPOAE level (dB SPL)			
	Right ear	**Left ear**	**Overall**	**p**
Study group	2.6 (2.03)	2.2 (1.88)	2.3 (2.01)	0.23
Control group	4.1 (2.48)	3.7 (1.92)	3.97 (2.06)	
p	0.007	0.011	0.013	
Confidence interval	(0.05-2.95)	(0.29-2.71)	(0.37-2.97)	

DPOAE; distortion product otoacoustic emission

tinnitus is still not completely elucidated. The purpose of this study was to investigate whether DPOAE could be used to verify cochlear and OHCs function in chronic bilateral tinnitus patients with normal hearing, assuming that the function of OHCs may play a role in the generation of tinnitus. Therefore, we examined DPOAE in the frequency range of 0.5−10 kHz with three points per octave to the estimation of OHCs function in subjective, constant, chronic, and bilaterally tinnitus patients with normal hearing. Performing DPOAE with this method allowed us to examine subtle areas and the higher frequency range of the cochlea. In addition, despite previous studies that performed DPOAE up to 8 kHz, we evaluated it up to 10 kHz to determine whether measurement of DPOAE at 10 kHz adds any value in determining the differences in the cochlear function between patients with and without tinnitus. The main findings of the current study indicated that although DPOAE level at a frequency of 10 kHz was not significantly different between the groups, but DPOAE levels at frequencies of 2500, 5000, and 6298 Hz were lower significantly in normal hearing subjects with tinnitus compare to non-tinnitus control subjects. Since the measurement of DPOAE at 10 kHz did not provide more information about the cochlear function between people with and without tinnitus, measurement of DPOAE up to 8 kHz frequency may be sufficient in this population. Furthermore, in our findings, there were no statistically significant differences in DPOAE level in both groups between the right and left ear. Sztuka et al. recorded DPOAE amplitude with two points per octave and fine structure registration at frequencies of 1001−6995 Hz in three groups of tinnitus patients with normal hearing (those with hyperacusis, those with misophonia, and those with neither) and control group. In agreement with our findings, they reported there were no statistically significant differences in DPOAE amplitude in all tinnitus groups between the right and left ear. The lack of difference between the ears may be because tinnitus may affect both ears almost equally. However, contrary to our results, they found markedly higher DPOAE amplitudes in the group of tinnitus patients without hearing loss suggest that tinnitus may be caused by increased motility of the OHCs induced by decreasing efferent fiber activity, and not by OHC failure [25]. This discrepancy between our results and Sztuka et al. may be due to the existence of hyperacusis in tinnitus patients of Sztuka study, which is a term that used to describe intolerance to everyday sounds that cause significant distress and impairment in social, occupational, recreational, and other day-to-day activities [26]. In addition, our results do not agree with the results obtained by Gouveris H et al. study that used DPOAE at frequencies of 700−6300 Hz in normal hearing or minimal hearing loss subjects with acute tonal tinnitus, which were aged between 16−69 years. They reported that ears in which acute

tinnitus is presently exhibited relatively increased amplitudes of DPOAE at high frequencies (4–6.3 kHz) when compared with the group of healthy ears, and relatively decreased DPOAE amplitudes at mid frequencies (1650–2400 Hz) [27]. This inconsistency between our results and Gouveris et al. results may be due to the presence of an acute progressive lesion of the cochlea, given that all of their tinnitus patients had acute symptoms or reflect differences in characteristics of studies populations. For instance, in their sample tinnitus pitch was mainly matched to 4 or 6 kHz compared to our sample that majority of patients matched the pitch of tinnitus to 6 and 8 kHz. In the present study, DPOAE level in the frequency of tinnitus was significantly lower in SG than CG. This finding was in line with Mokrian et al. study that used DPOAE at frequencies of 1000 to 8000 Hz in tinnitus patients with normal hearing, they reported lower DPOAE amplitude in the frequency of tinnitus in patients with tinnitus and normal hearing may be due to cochlear dysfunction [18]. Lower DPOAE level in the frequency of tinnitus may be caused by differential damage of outer and inner hair cells at a tinnitus pitch portion of the basilar membrane in the cochlea. Moreover, Jestreboff and Hazell believed that abnormal DPOAE in the frequency of tinnitus seemed relate to abnormal OHCs activity [9]. Our results are consistent with the results obtained by these studies; Ami et al. recorded DPOAE at frequencies of 0.5, 1, 2, 4, and 8 kHz in 4 groups of patients (tinnitus patients with hearing loss, tinnitus patients without hearing loss, non-tinnitus patients with hearing loss and control group), they reported that reduced outer hair cell activity, as detected by reduced DPOAE levels, may manifest as tinnitus even before there would be a shift in the hearing threshold [16]. Emadi et al. performed DPOAE at frequencies of 1000−8000 Hz in normal hearing subjects with and without tinnitus, they revealed decreased DPOAE amplitude in tinnitus participants compare to non-tinnitus participants with normal hearing and stated there was a direct relationship between OHCs dysfunction and tinnitus in normal hearing subjects [17]. Furthermore, Abo Jamous used DPOAE at frequencies of 750−6000 Hz, Fabijanska recorded DPOAE at frequencies of 0.5−9 kHz and Modh performed DPOAE at frequencies of 500−8000 Hz in tinnitus patients with normal hearing, they all reported a significant decrease in DPOAE amplitude of normal hearing tinnitus patients when compared to the non-tinnitus normal hearing subjects [28-30]. The decrease in the DPOAEs level indicates dysfunction of the OHC. This dysfunction may be due to discordant between intact IHCs and damaged OHCs. OHCs are more prone to damage and when it occurs, they fail to perform the inhibition over the IHC function. Although last theories suggest that this loss of IHC inhibition results then in tinnitus [31]. Recently, Knipper et al. suggested that loss of the critical drive in the fast auditory fibers that maintains baseline tonic inhibitory Parvalbumin positive interneurons network activity may cause an increase in spontaneous firing rates in central auditory circuits and impair input for specific contrast amplification in affected frequency-specific auditory regions, resulting in tinnitus [32]. Tinnitus patients with normal hearing may have damage not only in OHCs, but also in IHCs [33], synapses between IHCs. and the auditory nerve fibers [34] and efferent auditory nerve fibers [35] that DPOAE alone cannot determine the presence of damage in these areas. For these reasons, it could be postulated that OHCs damage may be present together with other subclinical pathologies, such as cochlear neuropathy, cochlear synaptopathy, and loss of high threshold fibers of auditory afferent nerves, may either contribute in resulting in tinnitus. Therefore, it is suggested that future studies using by auditory brainstem responses or Electrocochleography to assess auditory nerve function or recognize cochlear synaptopathy [34,36] and threshold equalizing noise test to recognize dead region in IHCs [37,38] along with DPOAE addressed these postulations.

Our study had certain limitations. Samples selected by convenience sampling that maybe makes our study at high risk for selection bias. Although the hearing thresholds in the control

group were almost better than the study group and there was no significant difference between the two groups, a larger sample size is needed to address this issue. In addition, we did not perform extended-high frequency audiometry, so the use of this test was needed to evaluate higher frequency regions.

Conclusion

We concluded that measurement of distortion product otoacoustic emission (DPOAE) at 10 kHz did not add more value in determining the differences in the cochlear function between patients with and without tinnitus, so it is only needed to measure DPOAE up to 8 kHz. Decrease of DPOAE level in the frequency of tinnitus and some certain frequencies in patients who have tinnitus and normal hearing, suggesting that limited areas of outer hair cells (OHCs) damage in the cochlea, which be detected by DPOAE but not by conventional audiometry that indicates DPOAE is a useful tool for assessment of OHCs function. In addition, it can be postulated that there is an association between tinnitus and OHCs dysfunction, which denotes that OHCs of the cochlea are involved in the generation of tinnitus. Further studies using a test battery would be required for evaluation of peripheral hearing status and mechanisms involved in the generation of tinnitus.

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Conflict of interest

The authors declared no conflicts of interest.

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