European Archives of Oto-Rhino-Laryngology (2019) 276:3013–3019
https://doi.org/10.1007/s00405-019-05585-4

OTOLOGY

The relationship of high-frequency distortion product otoacoustic emission (DPOAE) values with hematological parameters in tinnitus patients

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Received: 13 May 2019 / Accepted: 23 July 2019 / Published online: 1 August 2019

Abstract

Purpose In this study, we aimed to investigate whether there is any positive or negative correlation between high-frequency distortion product otoacoustic emission (DPOAE) values and mean platelet volume (MPV) and neutrophil/lymphocyte ratio (NLR) in tinnitus patients.

Methods The study was performed with 52 volunteers (27 females, 25 males) aged between 35 and 50 years who presented with tinnitus to the otolaryngology outpatient clinic of a tertiary care center. Pure voice audiometric examination, DPOAE measurement, complete blood count values of the study participants were examined.

Results In both ears, a significant and negative correlation was observed between 4000 and 8000 Hz airway and 4000 Hz bone conduction pathways with NLR rates ($p < 0.05$). A statistically significant relationship was found between the bone conduction pathway PTA and discrimination values for both ears and NLR s ($p < 0.05$). A positive correlation was detected between NLRs and DPOAE measurements recorded at 4444 Hz, 5000 Hz, 8000 Hz, 8889 Hz, 10,000 Hz and 11,429 Hz frequencies in the right and 4444 Hz, 5000 Hz, 6154 Hz, 8000 Hz, 10,000 Hz and 11,429 Hz frequencies in the left ears, respectively ($p < 0.05$).

Conclusions We concluded that there is a significant correlation between high-frequency pure tone audiometry measurements and high frequency DPOAE measurements and NLR. Further studies are needed to determine the utility of NLR as a marker for the recognition and follow-up of hearing loss in patients with tinnitus.

Keywords Tinnitus · Auto-acoustic emission · DPOAE · Neutrophil/lymphocyte ratio

Introduction

Tinnitus is the perception of sound without any audible warning signal. Tinnitus affects the quality of life negatively and it can be observed in patients with hearing loss [1]. In 30% of the patients with tinnitus, hearing levels were shown to be within normal limits [2]. In tinnitus patients, the pathology may involve the peripheral hearing pathways, cochlear and retrocochlear regions or more than one region. Therefore, audiometric assessments to be performed alone may not be sufficient to determine the location of the pathology [1]. The relationship between normal hearing threshold and the presence or absence of cochlear or retrocochlear abnormalities remains unclear [1].

Otoacoustic emission (OAE) measurement of distortion product is shown as the main method in the evaluation of cochlear activity in tinnitus patients [3]. Significant decreases in distortion product otoacoustic emission (DPOAE)amplitudes are detected in patients with complaints of tinnitus [4]. In a study, it was shown that the amplitude values of tinnitus patients with normal hearing threshold detected using DPOAE test decreased to 93% and the amplitude values in tinnitus patients with hearing loss decreased to 96% [5].

Neutrophil lymphocyte rate (NLR) and mean platelet volume (MPV) are new inflammation and thrombosis markers easily calculated from complete blood count (CBC) results [6].

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Tinnitus is a heterogeneous disease with vague underlying pathology; however, inflammatory and ischemic processes are supposed to play a role [7]. The utility of MPV as a potential marker in patients with obstructive sleep apnea syndrome, sudden sensorineural hearing loss, and tinnitus had been studied [8]. It has been postulated that tinnitus might be linked with stress and related inflammation. Tinnitus patients had a significantly higher NLR compared to controls, which reminded a relationship between inflammation and tinnitus [9]. NLR serves as an inflammation marker in both cardiac and non-cardiac diseases [10, 11]. Recently, elevated NLR was detected in patients with sudden hearing loss, Bell's palsy, and tinnitus, and it seemed to be a poor prognostic factor [9, 12–14]. There are controversial data on NLR in tinnitus patients and NLR is supposed to be a clinical indicator for tinnitus patients [6, 9].

Although there are studies on MPV and NL in patients with tinnitus, any one of these studies have not evaluated the correlation between high-frequency DPOAE measurements and hematological biomarkers such as MPV and NLR. In this study, considering the inflammation process in patients and changes in the amplitude readings of an electrophysiological hearing evaluation test known as DPOAE, we aimed to investigate whether or not increased inflammation in tinnitus patients had any effect on DPOAE amplitudes. Therefore, we aimed to examine whether there is any positive or negative correlation between high-frequency DPOAE values with MPV and NLR in tinnitus patients.

Material and methods

In this prospective study, permissions were obtained from the local ethics committee of clinical studies (2019-42), and necessary consent forms were signed by the participants. Our study was carried out with 52 volunteers aged 35–50 years who were admitted to otolaryngology outpatient clinics of our hospital with the complaint of tinnitus.

Pure tone audiometry (PTA) examination, tympanometric examination results, DPOAE measurements, complete blood count, B12 vitamin levels, liver function tests (AST, ALT, total bilirubin, direct bilirubin) and renal function tests (urea, creatinine) were evaluated. Patients who had pathology in other hematological parameters except the complete blood count parameters were excluded from the study. In addition, age, gender, additional diseases and the duration of tinnitus complaints were questioned. Participants with tinnitus complaints for at least one year were included in the study. Participants with a history of neck pathology and head trauma, systemic diseases, malignancy or any inflammatory disease were excluded from the study. Participants underwent a complete ENT examination. Patients with any pathology including infections were excluded from the study. In addition, all patients with any additional disease that would trigger the systemic inflammatory process were excluded from the study. Patients with a history of chronic drug use for any reason within the last one year were excluded from the study. In addition, patients with mixed type and conductive hearing loss were excluded from the study. Only patients with hearing loss within normal limits and sensorineural hearing loss were included in the study. Contrast-enhanced temporal magnetic resonance imaging examinations were routinely requested from participants. Patients with abnormal magnetic resonance imaging results were excluded from the study.

Blood samples were drawn routinely from the antecubital vein. Samples were collected in ethylenediaminetetraacetic acid (EDTA) tubes. CBC and biochemical analyses were made. To ensure standardization of CBC analyses, the same device was used for all evaluations. (Abbott Cell-Dyn 3700, Abbott Laboratories, Abbott Park, IL, USA).

Audiometric evaluation was performed by the same audiometrist, also to ensure standardization (Type A-E Speech audiometer, AC40, Interacoustics A/S, DK-5610 Assens, Denmark). In pure tone audiometry, airway, and bone conduction pathways of both earswere evaluatedat 250 Hz, 500 Hz, 1000 Hz, 2000 Hz, 4000 Hz, 8000 Hz, and at 250 Hz, 500 Hz, 1000 Hz, 2000 Hz, and 4000 Hz frequencies, respectively.

DPOAE ölçümleri için de standardizasyon amacıyla aynı odyometrist tarafından yapıldı ve aynı cihaz kullanıldı (Echoport ILO292 USB-I Otodynamics, Ltd, UK).

DPOAE measurements were first routinely calibrated. DPOAE was measured using a general diagnosis nonlinear click stimulus. The f2 and f1 frequency ratio (f2/f1) was evaluated as 1.22. Stimulus level was accepted as L1 for f1 and L2 for f2. L1–L2 was kept at 10 dB sound pressure level (SPL) (L1 = 65, L2 = 55). DPOAE readings were measured in the external ear canal with a microphone at 2f1–f2 frequency. For DPOAE, hearing thresholds for both ears were calculated for 988 Hz, 1270 Hz, 1778 Hz, 2222 Hz, 2500 Hz, 3200 Hz, 4444 Hz, 5000 Hz, 6154 Hz, 8000 Hz, 8889 Hz, 10,000 Hz, 11,429 Hz frequencies.

For determining DPOAE values, emission value of 3 dB SPL higher than the noise level for each frequency was considered the threshold value.

The correlation between DPOAE values and MPV and NLR were evaluated withineach group. MPV, NLR, audiogram, and DPOAE values were also compared statistically between groups.

Statistical analysis

Data were analyzed using the IBM Statistical Package for Social Sciences v18 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were expressed in number and

percentage for sex, mean ± standard deviation values for MPV and NLR levels. Correlation analyses were performed for the relationship between hematological parameters and hearing levels, and expressed as correlation coefficient "*r*". The correlation coefficients were evaluated as the presence of a very strong (1.00–0.90): strong (0.89–0.70): moderate (0.69–0.50), and poor (0.49–0.30) correlation. $P < 0.05$ was considered statistically significant.

Results

The mean age of the participants was 41.62 ± 4.76 (min: 35–max: 50) years. Of the 52 participants, 27 (51.9%) were female, and 25 (48.1%) were male. Twenty-four (46.2%) patients had hearing loss in their right, and 19 (36.5%) patients had hearing loss in their left ears. Bilateral hearing loss was seen in 30.8% ($n = 16$) of the patients. Twenty-seven out of 52 participants (52%) had hearing loss.

There were no significant differences in terms of NLR and MPV values between the right and left ears ($p > 0.05$) (Table 1).

The pure tone audiometry is used for the evaluation of NLR at frequencies of 250 Hz, 500 Hz, 1000 Hz, 2000 Hz, 4000 Hz and 8000 Hz for both ears, and at 250 Hz, 500 Hz, 1000 Hz, 2000 Hz, and 4000 Hz frequencies for bone path measurements. Considering the correlation between MPV rates; in both ears, a significant and negative correlation was found between 4000 and 8000 Hz airway and 4000 Hz bone path values with NLRs ($p < 0.05$). However, no significant correlation was found between MPV measurements and frequency values ($p > 0.05$). Negative correlation coefficients between NLR ratios and frequency values were evaluated; and correlation coefficients at frequencies of 4000 Hz, were *r*: −0.334, *r*: −0.352 for the right, and *r*: −0.343, and *r*: −0.473 for the left ear, respectively. For bone conduction pathways correlation coefficients at 4000 Hz frequency were r: −0.339) for the right, and *r*: −0.414 for the left ear. A negative but a weak correlation was found between each frequency value and NLR (Table 2).

In addition, when the participants were evaluated in terms of PTA averages, and discrimination values; any correlation was not seen between airway PTA values and NLR and MPV measurements for both ears ($p > 0.05$). A significant

Table 1 Statistical analysis of NLR and MPV levels according to the presence of hearing loss

	NLR (mean ± standard deviation)	*p*	MPV (mean ± standard deviation)	*p*
Right ear				
No	1.99 ± 0.61	0.099	7.52 ± 1.93	0.607
Yes	1.64 ± 0.71		7.78 ± 1.29	
Left ear				
No	1.89 ± 0.86	0.309	7.52 ± 1.73	0.857
Yes	1.53 ± 0.47		7.84 ± 1.02	

NLR neutrophil lymphocyte ratio, *MPV* mean platelet volume

Table 2 Statistical relationship between each frequency value in audiometric evaluation data and NLR and MPV ratios

	Right ear				Left ear			
	NLR		MPV		NLR		MPV	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*
Air conduction pathway								
250 Hz	0.115	0.428	−0.017	0.903	0.048	0.743	−0.113	0.429
500 Hz	−0.146	0.313	−0.049	0.730	−0.043	0.768	−0.114	0.426
1000 Hz	−0.017	0.907	0.026	0.854	−0.050	0.732	0.044	0.762
2000 Hz	−0.166	0.249	0.188	0.187	−0.188	0.192	0.073	0.608
4000 Hz	−0.334	0.018	0.175	0.219	−0.343	0.015	0.013	0.925
8000 Hz	−0.352	0.012	0.113	0.429	−0.473	0.001	0.029	0.841
Bone conduction pathway								
500 Hz	−0.175	0.223	−0.130	0.365	−0.032	0.826	−0.176	0.216
1000 Hz	−0.112	0.437	−0.085	0.555	−0.093	0.519	−0.088	0.538
2000 Hz	−0.219	0.127	0.062	0.665	−0.252	0.078	0.022	0.880
4000 Hz	−0.339	0.016	0.101	0.479	−0.414	0.003	−0.068	0.636
Air-way PTA	−0.244	0.087	0.138	0.335	−0.252	0.077	−0.008	0.957
Bone-way PTA	−0.318	0.024	0.060	0.675	−0.352	0.047	−0.026	0.857
Discrimination	0.338	0.019	−0.016	0.916	0.322	0.037	0.112	0.447

Underlined datas represent statistically significant results

r correlation coefficient, *PTA* pure tone average, *NLR* neutrophil lymphocyte ratio, *MPV* mean platelet volume

correlation is seen between bone pathway PTA values and discrimination values and NLR rates for both ears ($p < 0.05$). However, there was no correlation between bone pathway PTA values and discrimination values and MPV rates for both ears ($p > 0.05$). When the coefficients of correlation between NLRs and bone pathway PTA values were evaluated; correlation coefficients for bone path PTA values for the right (r: −0.318), and the left ears (r: −0.352) were determined as indicated. These findings suggest us that there is a negative but weak correlation between bone path PTA values and NLRs (Table 2). In addition, when the coefficients of correlation between NLRs and discrimination values were assessed; correlation coefficients for discrimination values for the right (r: 0.338), and the left ear (r: 0.322) were determined. These findings show a positive but poor correlation exists between the discrimination values and NLRs (Table 2)**.**

In correlation analysis performed between DPOAE measurement results at frequencies of 988 Hz, 1270 Hz, 1778 Hz, 2222 Hz, 2500 Hz, 3200 Hz, 4444 Hz, 5000 Hz, 6154 Hz, 8000 Hz, 8889 Hz, 10,000 Hz, 11,429 Hz, and NLR, and MPV rates calculated for both ears any correlation was not detected at 988 Hz, 1270 Hz, 1778 Hz, 2222 Hz, 2500 Hz, 3200 Hz and 6154 Hz frequencies for the right ($p > 0.05$), and at 988 Hz, 1270 Hz, 1778 Hz, 2222 Hz, 2500 Hz, 3200 Hz and 8889 Hz frequencies for the left ears ($p > 0.05$). However, a significant, and a positive correlation was detected between NLRs and DPOAE measurement results at 4444 Hz, 5000 Hz, 8000 Hz, 8889 Hz, 10,000 Hz, and 11,429 Hz frequencies in the right, and at 4444 Hz, 5000 Hz, 6154 Hz, 8000 Hz, 10,000 Hz and 11,429 Hz in the left ears ($p < 0.05$) (Table 3).

The correlation coefficients between NLRs and DPOAE frequency values were evaluated; and correlation coefficients for the right ear at frequencies of 4444 Hz (r: 0.315), 5000 Hz (r: 0.338), 8000 Hz (r: 0.357), 8889 Hz (r: 0.456), 10,000 Hz (r: 0.312), and 11,429 Hz (r: 0.364).For the left ear the correlation coefficients were determined at frequencies of 4444 Hz (r: 0.315),5000 Hz (r: 0.385), 6154 Hz (r: 0.438), 8000 Hz (r: 0.468), 10,000 Hz (r: 0.382) and 11,429 Hz (r: 0.406). A positive but weak correlation was found between each frequency value and NLR(Table 3). In addition, the audiometric evaluation data of the participants are given in Table 4.

Discussion

Correlation between DPOAE values and the hematological biomarker, NLR, was found in patients with tinnitus. Studies have shown that the inflammatory process may play a role in the pathophysiology of tinnitus. These inflammatory processes result in elevated levels of various inflammatory markers which can be detected in blood [9]. NLR can be used as a marker of poor prognosis in many diseases and is considered an important indicator of long-term mortality and morbidity [15, 16]. NLR is also used as a prognostic indicator in many otolaryngologic pathologies including facial paralysis and sudden idiopathic hearing loss [13, 17]. MPV can also be used as a biomarker and can be measured

Table 3 Statistical relationship between the frequency value in DPOAE measurement and NLR, MPV ratios

Right ear[a]	NLR		MPV		Left ear[b]	NLR		MPV	
	r	*p*	*r*	*p*		*r*	*p*	*r*	*p*
988 Hz	0.059	0.683	−0.107	0.455	988 Hz	0.091	0.531	0.109	0.445
1270 Hz	−0.037	0.800	−0.245	0.083	1270 Hz	0.151	0.295	0.003	0.982
1778 Hz	0.232	0.104	−0.056	0.697	1778 Hz	0.041	0.779	0.062	0.667
2222 Hz	0.175	0.224	−0.127	0.376	2222 Hz	0.126	0.384	−0.020	0.887
2500 Hz	0.125	0.387	−0.121	0.396	2500 Hz	0.043	0.764	−0.049	0.732
3200 Hz	0.175	0.223	−0.098	0.496	3200 Hz	0.153	0.288	−0.090	0.530
4444 Hz	0.315	0.026	0.019	0.895	4444 Hz	0.315	0.026	−0.055	0.701
5000 Hz	0.338	0.016	0.128	0.371	5000 Hz	0.385	0.049	−0.221	0.119
6154 Hz	0.123	0.052	0.119	0.407	6154 Hz	0.438	0.031	−0.007	0.960
8000 Hz	0.357	0.042	0.004	0.976	8000 Hz	0.468	0.023	−0.048	0.736
8889 Hz	0.456	0.036	−0.056	0.699	8889 Hz	0.172	0.062	−0.162	0.257
10,000 Hz	0.312	0.044	−0.179	0.213	10,000 Hz	0.382	0.025	0.112	0.434
11,429 Hz	0.364	0.034	0.027	0.854	11,429 Hz	0.406	0.003	0.227	0.109

Underlined datas represent statistically significant results

r Correlation coefficient, *PTA* pure tone average, *NLR* Neutrophil lymphocyte ratio, *MPV* mean platelet volume, *DPOAE* distortion product otoacoustic emission

[a]Right ear DPOAE measurement frequencies

[b]Left ear DPOAE measurement frequencies

Table 4 Audiometric evaluation data of participants

	Mean ± standard deviation	
	Right ear	Left ear
Air conduction pathway		
250 Hz	18.37 ± 9.59	18.65 ± 16.09
500 Hz	16.73 ± 8.85	13.37 ± 14.20
1000 Hz	17.02 ± 11.81	14.04 ± 15.84
2000 Hz	20.00 ± 17.52	19.13 ± 23.15
4000 Hz	37.21 ± 22.52	37.02 ± 26.85
8000 Hz	45.58 ± 25.10	43.56 ± 28.03
Bone conduction pathway		
500 Hz	11.35 ± 7.28	11.06 ± 11.22
1000 Hz	12.50 ± 10.17	11.73 ± 13.02
2000 Hz	16.63 ± 16.71	16.63 ± 19.45
4000 Hz	32.02 ± 22.12	31.73 ± 24.09
Air-way PTA	22.71 ± 12.37	21.00 ± 17.73
Bone-way PTA	17.96 ± 11.70	17.23 ± 14.69
Discrimination	87.92 ± 13.82	86.37 ± 16.29

PTA pure tone average

in complete blood count; increases or decreases in MPV levels reflect inflammatory processes, though results are conflicting [18–20]. One study showed that tinnitus patients had significantly increased MPV levels compared to the control group [20], while another study found there was no significant difference between tinnitus patients and the control group according to MPV [9]. The same study emphasized significantly increased NLR in tinnitus patients compared to the control group. The authors of that study concluded that NLR could be used as an important biomarker in tinnitus patients [9].

Results on the potential use of NLR as a predictive or prognostic indicator of tinnitus are also conflicting. The number of patients, presence of systematic diseases, or individual patient characteristics may affect the results of these studies. Studies with heterogeneous patient groups show that results are not significant and that NLR cannot be used as a prognostic predictor [6].

In this study, tinnitus patients were evaluated with respect to accompanying hearing loss. Accordingly, the presence of hearing loss was found to have no effect on MPV and NLR.

Audiological evaluations have shown that normal audiological values do not accurately reflect the auditory pathway [4]. Moreover, one study found that tinnitus patients, even with normal hearing thresholds, performed worse than control groups at high frequencies [5]. In pure-tone audiometry performed at 250–8000 Hz frequency range for both ears, decreased threshold levels frequency was observed at 4000 and 8000 Hz. The literature has indicated that tinnitus may affect hematological parameters and that decreased hearing threshold levels may be observed, especially at high frequencies [4]. However, we did not encounter any study evaluating the relationship between hematological parameters and frequency measurements of pure tone audiometry. The main purpose of this study was to determine whether or not there was any relationship between hematological and audiological parameters. According to our results, the relationship between each frequency and NLR and MPV values was revealed in pure tone audiometry. In both ears, a negative but weak correlation existed between 4000 and 8000 Hz airway and 4000 Hz bone path frequencies and NLR values. Discrimination rates were also positively correlated with NLR values.

Although it was stated that spontaneous OAE could be seen in tinnitus patients, there was no relationship between severity of tinnitus and OAEs. However, a correlation between DPOAE values and tinnitus has been shown [21]. In this study, tinnitus was not grouped according to severity. Despite various inconsistencies, OAE values are known to be useful for investigating cochlear mechanisms in tinnitus patients. Studies have shown that abnormal DPOAE levels are closely related to tinnitus [4]. One study showed that there were significant differences in DPOAE values detected between 4000 and 7000 Hz in patients with tinnitus compared to the control group [22]. In another study, decreased DPOAE responses at high frequencies was observed in tinnitus patients with hearing loss [23]. Decreased DPOAE amplitudes were also more pronounced in the mid- and high-frequency ranges in patients with tinnitus [5, 24, 25]. In contrast, another study showed significantly increased DPOAE amplitudes in the 4000–6000 Hz frequency range in tinnitus patients [26]. According to the literature, there are clearly conflicting opinions on DPOAE amplitude levels in tinnitus patients. These differences are due to the role of different mechanisms according to the physiopathology of tinnitus. In this study, evaluations were made up to 11,429 Hz DPOAE frequency.

Furthermore, we have not encountered any studies examining the relationship between DPOAE frequency values and hematological parameters, while there are many studies in the literature examining DPOAE values in tinnitus patients. This, once again, emphasizes the importance of our study. We evaluated both the DPOAE test results between 988 and 11429 Hz frequencies and also the correlation of each frequency with NLR and MPV values. According to our results, we found a positive correlation with NLR at ≥ 4444 Hz frequencies for both ears.

In this study, tinnitus patients were not divided according to disease severity. With the assessment of the severity of the disease, the effects of both NLRs and MPVs on each frequency can change and lead to different outcomes. In addition, correlation analysis based on age groups can be useful in demonstrating the relationship between high-frequency pure tone audiometry measurements, DPOAE measurements

at high frequencies, NLR, and MPV values. The impact of age on the correlation between frequency values and hematological parameters can also be demonstrated.

In conclusion, elevated NLR due to chronic inflammation and visible DPOAE amplitude changes in tinnitus patients show that there is an interaction between hematologic parameters and DPOAE amplitudes. In this study, we also established that there was a correlation between NLR measurements and high-frequency DPOAE amplitudes. It was also established that there is a relationship between high-frequency pure tone audiometry measurements and high-frequency DPOAE measurements and NLR which can be used as a hematological biomarker.

Acknowledgements No financial support was received for this paper.

Funding No financial support was received.

Compliance with ethical standards

Conflict of interest Akif Gunes declares that he has no conflict of interest. Elif Karali declares that she has no conflict of interest. Ahmet Ural declares that he has no conflict of interest. Fatih Ruzgar declares that he has noconflict of interest. Tugba Bayatkara declares that she has no conflict of interest.

Ethical approval This study includes human participants and this study has been carried out in accordance with ethical standards and the Helsinki declaration.

Informed consent Informed consent was obtained from all participants.

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