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Research Article

Ischemia modified albumin level and thiol/disulfide homeostasis in the etiology of tinnitus

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Abstract

Objectives: Although many theories about the etiology of tinnitus have been proposed, it has not been fully clarified. In this study, we investigated the role of ischemia in the etiology of tinnitus.

Methods: A total of 90 participants, 50 tinnitus patients and 40 controls, were included in this study. Total thiol (TT), native thiol (NT), NT/TT ratio, disulfide, disulfide/TT ratio, disulfide/NT ratio, ischemia-modified albumin (IMA), and IMA/albumin ratio (IMA/AlbR) values of tinnitus patient group and controls were compared and receiver operating characteristic (ROC) analyses conducted.

Results: IMA (0.767±0.06) and IMA/AlbR (17.71±2.46) values were statistically significantly higher in the tinnitus group than in the control group (0.742±0.06 vs. 16.00±2.48 and p=0.040 vs. p=0.002, Independent Samples test). No statistically significant difference was observed between the groups for the other parameters. While albumin was presenting a perfect positive correlation with TT and NT, IMA showed rugged negative parallelism with NT and TT, similar to that of IMA/AlbR. According to ROC analysis, a cut-off value of 14.29 was found to be statistically significant for IMA/AlbR in distinguishing patients with tinnitus from the controls (sensitivity of 96%, specificity of 32.5%, AUC: 0.676, and p=0.002).

Conclusion: In the present study, in the tinnitus group, higher values of IMA and IMA/AlbR, which are markers of ischemic status, support the theory specifying that ischemia has an influential role in the etiology of tinnitus.

Keywords: Disulfide, IMA, thiol/disulfide homeostasis, tinnitus

Many theories about the formation of tinnitus have been put forward. Some of these theories are the hyperactivity in the auditory nuclei of the brainstem, damage of the cochlear hair cells, increase in the spontaneous activity of the auditory nerve fibrils, ischemic changes occurring in the inner ear, and cochlear damage resulting in a decrease in the suppressive effect of the central auditory cortex on the upper neural activities [1].

A change at the N-terminal end of albumin occurs under ischemic conditions, and it transforms into ischemia-modified albumin (IMA) having decreased capacity for binding cobalt, copper, and nickel. Serum IMA levels have been detected to be higher in the tinnitus group than in the control group for many diseases such as acute coronary syndrome, pulmonary embolism, cerebrovascular events, peripheral vascular disease, and mesenteric ischemia [2, 3].

Thiol/disulfide homeostasis (TDH) is a marker of oxidative stress. Abnormal TDH plays an important role in the pathogenesis of numerous diseases such as cancer, coronary artery disease, chronic kidney disease, diabetes mellitus, rheumatoid arthritis, uterine myoma, celiac disease, basal cell carcinoma, intrahepatic cholestasis of pregnancy, idiopathic Parkinson's disease, Alzheimer's disease, preeclampsia, acute appendicitis, seborrheic dermatitis, migraine, age-related macular degeneration, and erectile dysfunction [4-6].

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The goal of the current study is to ascertain the role of ischemia in the etiology of tinnitus by using the parameters of IMA, used as a marker of ischemia, and TDH, used as an oxidative stress marker. Only a limited number of studies on this subject are found in the literature.

Materials and Methods

In this study, 90 participants [M: 42 (47%) and F: 48 (53%)] aged between 18 and 66 years, who applied to the outpatient clinic of otorhinolaryngology, were included. Two groups were formed: patient group and control group. The patient group (tinnitus) included 50 patients with tinnitus (M: 24; F: 26), who applied due to tinnitus problems and had a normal audiological examination and audiometry. Forty people (M: 18; F: 22), who applied to the outpatient clinic for other reasons but detected with no disease were included in the control group. Visual Analogue Scale (VAS) test was applied to the tinnitus group [7]. The exclusion criteria of the study were: having anatomic problems related to the external ear or the inner ear, having any ear-related disease or history of disease other than tinnitus, having a chronic systemic disease (such as hypertension and diabetes mellitus), and being under the age of 18. The approval of the ethics committee of the KTO Karatay University Faculty of Medicine (the decision with a date of October 24, 2018, and no. 2018/011) was taken for the study.

From both groups, 5 mL of venous blood samples was drawn to serum separation tubes with gel. The supernatant was separated after centrifuging the samples at 3000g for 10 min. The supernatant sera were kept until the study day at -80°C. All were thawed and analyzed on the same day. Albumin, IMA, TT, and NT levels were determined from the samples.

Albumin and IMA measurement

Serum albumin levels (albumin commercial kit, Beckman Coulter Inc., Brea, CA) were measured using an Olympus AU 400 (Olympus Life and Material Science Europa GmbH, Hamburg, Germany) autoanalyzer. Serum IMA levels were analyzed using the albumin cobalt binding test, a rapid colorimetric method developed by Bar-Or et al. [8] IMA results were determined in absorbance units.

Measurement of NT and TT levels: Serum TT and NT levels were measured on a Cobas 501 (Roche Diagnostics, Indianapolis, IN) using the method developed by Erel and Neselioglu, which primarily reduces disulfide bonds with sodium borohydride (NaBH4) to develop free functional thiol groups. The unused reductant NaBH4 is consumed with formaldehyde. The total amount of thiol is measured using the modified Ellman reactive. The amount of NT was measured using the same method without any reduction process. The outcomes were obtained as μmol/L [9]. From the results obtained, IMA/albumin ratio (IMA/AlbR), disulfide levels [(TT-NT)/2], disulfide/NT ratio (%), disulfide/TT ratio (%), and NT/TT ratio (%) were calculated [9, 10].

Statistical analysis

SPSS 25.0 (SPSS 25.0 Statistics, IBM) and MedCalc (Trial Version, MedCalc) statistical package programs were used for data evaluation. Variables were assessed after the homogeneity and normality of variance prerequisites were checked (Shapiro Wilk and Levene's test). During data analysis, the differences between two dependent groups were assessed by using "Independent Samples T Test, (Student t-test)" then the prerequisites of parametric test were met, and by using "Mann-Whitney U Test" when they did not met the said prerequisites. Mean (±standard deviation), median (±interquartile range), percentage, and frequency values of the variables were used. In the correlation analysis, Pearson's correlation was conducted for the tests meeting the parametric prerequisites, and Spearman's correlation analysis was performed for the nonparametric tests. Receiver operating characteristic (ROC) curve analysis was used to evaluate the clinical significance of the markers regarding the prediction of tinnitus. Youden's index (J=sensitivity+specificity-1), coinciding with the closest point to the upper left corner on the ROC graph and reflecting the highest total value of sensitivity and specificity, was used to determine the cut-off value. The value of $p<0.05$ was accepted for the significance level of the tests.

Results

A total of 90 participants [M: 42 (47%) and F: 48 (53%)], between the ages of 18 and 66 years with an average age of 41.00 (±11.1) years, were included in the study. Fifty (M: 24; F: 26) of the participants with an average age of 42.48 (±11.30) years were included as the tinnitus group and 40 (M: 18; F: 22) with an average age of 39.15 (±10.60) years as the control group. VAS score of the tinnitus group was found to be 4.94±2.11. No statistically significant difference was determined between the groups in terms of age, gender, and serum albumin values ($p>0.05$, Independent Samples test).

When the data of both groups were examined, IMA (0.767±0.06) and IMA/AlbR (17.71±2.46) values of the tinnitus group were found to be statistically significantly higher than those of the control group (0.742±0.06 vs. 16.00±2.48 and $p=0.040$ vs. $p=0.002$, Independent Samples Test).

When assessing the TT, NT, disulfide, disulfide/NT ratio, disulfide/TT ratio, and NT/TT ratio values of both groups, no significant statistical difference was found ($p>0.05$, Independent Samples test). Table 1 shows the age, albumin, IMA, IMA/AlbR, NT and TT, disulfide, disulfide/NT ratio, disulfide/TT ratio, and NT/TT ratio results of the study group.

In the correlation analysis of the sample group, albumin presented a strong positive correlation with NT and TT, but IMA and IMA/AlbR showed a strong negative correlation with NT and TT. No other significant correlation was observed. Table 2 shows the results of the correlation analysis between albumin, IMA, and IMA/AlbR, and NT, TT, and disulfide. ROC analysis was conducted for diagnosing the threshold of tinnitus, and 96% sensitivity and

Table 1.Comparison of age, albumin, IMA, IMA/AlbR, native thiol, total thiol, disulfide, disulfide/native thiol ratio, disulfide/total thiol ratio, and native thiol/total thiol results of the sample group

Parameters	Tinnitus group n=50 (M=24, F=26)	Control group n=40 (M=18, F=22)	p#
Age (year)*	42.48 (±11.30)	39.15 (±10.60)	0.157
Albumin (mg/dL)*	4.61 (±0.42)	4.66 (±0.44)	0.170
IMA (ABSU)*	0.767 (±0.06)α	0.742 (±0.06)	0.040β
IMA/AlbR (%)*	17.71 (±2.46)α	16.00 (±2.48)	0.002β
Native Thiol (µmol/L)*	506 (±46)	524 (±59)	0.122
Total Thiol (µmol/L)*	550 (±48)	569 (±62)	0.107
Disulphide (µmol/L)*	21.91 (±4.91)	22.69 (±5.20)	0.472
Disulphide/Native Thiol ratio (%)*	4.35 (±1.01)	4.35 (±1.02)	0.996
Disulphide/Total Thiol ratio (%)*	3.99 (±0.86)	3.99 (±0.85)	0.998
Native Thiol/Total Thiol ratio (%)*	92.02 (±1.73)	92.01 (±1.71)	0.992

*: Values are given as mean(±sd); #p value for Independent Samples Test; α: Statistically significantly different from the control group (p<0.05); β: A statistically significant difference was found between the groups; IMA: Ischemia modified albumin; IMA/AlbR: IMA Albumin ratio; ABSU: Absorbance units.

Table 2. Results of the correlation analysis between albumin, IMA, and IMA/AlbR and native thiol, total thiol, and disulfide

Tests parameters	Native thiol (µmol/L)		Total thiol (µmol/L)		Disulphide (µmol/L)	
	r	p*	r	p*	r	p*
Albumin (g/dL)	**0.632**	<0.001β	**0.630**	<0.001β	0.141	0.184
IMA (ABSU)	**-0.581**	<0.001β	**-0.581**	<0.001β	-0.142	0.178
IMA/AlbR (%)	**-0.668**	<0.001β	**-0.665**	<0.001β	-0.143	0.178

*: Correlations pearson; β: A statistically significant correlation was found between the parameters; IMA: Ischemia modified albumin; IMA/AlbR: IMA Albumin ratio; ABSU: Absorbance units.

Table 3. ROC analysis results of the tests for distinguishing the tinnitus group from the control group

Tests parameters	Cut-Off	Sens	95% CI	Spec	95% CI	+LR	95%CI	-LR	95% CI	AUC	95%CI	p
IMA#	>0.678	100.00	92.9-100.0	20.00	9.1-35.6	1.25	1.1-1.5	0.00		0.597	0.489-0.699	0.110
IMA/AlbR(%)#	>14.29	96.00	86.3-99.5	32.50	18.6-49.1	1.42	1.1-1.8	0.12	0.03-0.5	0.676	0.569-0.771	0.002*
Native Thiol#	≤566.2	92.00	80.8-97.8	27.50	14.6-43.9	1.27	1.0-1.6	0.29	0.1-0.8	0.599	0.490-0.701	0.107
Total Thiol#	≤583.3	78.00	64.0-88.5	45.00	29.3-61.5	1.42	1.0-1.9	0.49	0.3-0.9	0.609	0.500-0.710	0.075
Disulphide#	≤27.45	92.00	80.8-97.8	20.00	9.1-35.6	1.15	1.0-1.4	0.40	0.1-1.2	0.517	0.409-0.624	0.784

#: Values of the groups were calculated using the ROC curve; *: P values are statistically significant (p<0.05); ROC: Receiver operating characteristic; Sens: Sensitivity; CI: Confidence interval; Spec: Specificity; LR: Likelihood rate; AUC: Area under the curve; IMA: Ischemia modified albumin; IMA/AlbR:IMA Albumin ratio.

32.5% specificity were found when the cut-off value was used as 14.29 for IMA/AlbR, which was statistically significant (AUC: 0.676 and p=0.002). The results of the ROC analysis are given in Table 3, and the ROC curve of IMA/AlbR is shown in Figure 1.

In this study, IMA and IMA/AlbR results in the tinnitus group were also high, supporting ischemia in the etiology of tinnitus.

Discussion

The prevalence of tinnitus in the population is 10-20%, and its incidence tends to increase with age and may be present in approximately one-third of the elders [1, 11]. Many theories have been proposed regarding the etiology of tinnitus, but its mechanism of formation is still not clear. The theory on ischemia in tinnitus is studied, and the drugs used in the treatment are primarily developed based on this theory. It is reported that trimetazidine provides a statistically significant benefit in the treatment of tinnitus. The use of trimetazidine, acting by regulating the energy metabolism in the ischemic cell and limiting the damages related to the free radicals, suggests that ischemia may also be an etiological factor in tinnitus [1, 12].

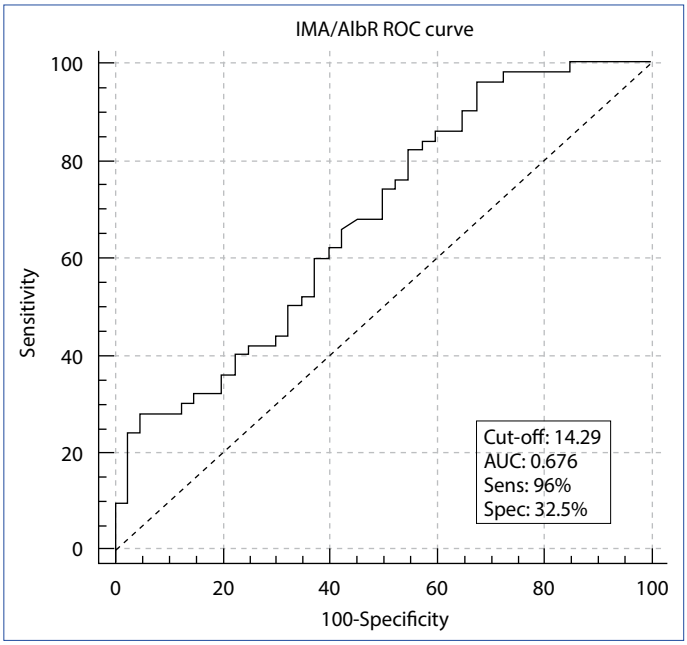

Figure 1. ROC curves for the detection of tinnitus: IMA/AlbR parameter.

IMA/AlbR: IMA Albumin ratio; ROC: Receiver operating characteristic; AUC: Area under the curve; Sens: Sensitivity; Spec: Specificity.

Any kind of hypoxic state occurring in the cell impairs the ability of albumin to bind with various metals and IMA is formed. The hypoxic environment causes an increase in the permeability of the cell membrane, acidosis, and damage related to the free radicals, and hence dysfunction in various functional proteins. IMA is a marker that is particularly associated with acute coronary syndrome, but it is not a tissue-specific marker. It has been shown that IMA levels increased in some chronic ischemic events such as cancer, systemic sclerosis, and end-stage renal failure. Several studies have shown that the increase in IMA is sensitive to diseases such as mesenteric ischemia, pulmonary embolism, stroke, and ovarian torsion. Also, it has been specified that IMA levels increase in strangulated hernia and get better when the obstruction is eliminated [13-16]. Only a limited number of studies stating the use of trimetazidine hydrochloride in cochlear vestibular symptoms, which acts by regulating the energy metabolism in the ischemic cell, are available. Cevik et al. conducted a study on 40 patients with tinnitus and found that a 3-month trimetazidine treatment caused a statistically significant decrease in the tinnitus complaints and VAS score of the patients, but the treatment did not provide a statistically significant change in the audiological tests [1, 17, 18]. Renda et al. [19], in their study including 17 patients with sudden hearing loss, found that the IMA levels were similar to those of the control group. They also determined no correlation between IMA and audiological tests. In their study on the etiology of tinnitus, Ensari et al. [20] found that apelin levels, which inhibit cell death and activate angiogenesis, were low in ischemic cases. In addition, they found a negative correlation between apelin levels and tinnitus severity. In our study, IMA and IMA/AlbR levels of patients with tinnitus were higher. These results suggest that ischemia is one of the most important factors in the etiology of tinnitus.

It has been reported in the literature that there is a close correlation between tinnitus and psychological diseases. Depression, anxiety, concentration disorder, irritability, and various psychiatric and personality problems are more common in patients with tinnitus [21, 22]. There are studies related to the IMA levels in psychiatric disorders. Karaaslan et al. [23] identified that the IMA levels of patients with major depression were found to be statistically significantly higher than those of healthy controls, and the elevation of IMA was positively correlated with the severity of depression. Brain tissue is extremely susceptible to ischemia due to high oxygen consumption and limited capacity for self-perpetuation. In ischemic situations, emotional changes may occur frequently. It is considered that one of the causes of accompanying psychiatric findings in tinnitus may be the same mechanism. Further studies should be conducted.

Recently, TDH has been intensively studied. In many oxidative stress situations where oxidant and antioxidant balance is impaired, TDH has been shown to change in the oxidant direction [24]. In patients with tinnitus, Koc et al. [11] found that serum paraoxonase and total antioxidant status levels were lower than the controls, and total oxidant status and oxidative stress index values were higher in the tinnitus group. Yalciner et al. [25] found that disulfide/NT and disulfide/TT levels were higher in patients with tinnitus than in the control group, but NT, TT levels, and NT/TT ratios were lower than in the control group. On the basis of these results, they asserted that TDH and oxidative stress are important in the etiology of tinnitus. A study about TDH and oxidative stress in patients with tinnitus was made by Celik et al. [26] A total of 70 subjects, including 35 tinnitus patients and 35 healthy individuals, participated in their study. The study showed that NT levels and NT/TT ratios were significantly lower in the tinnitus group than in the control group. Disulfide levels and disulfide/NT and disulfide/TT ratios were significantly higher in the patients. Both Celik et al. and Koc et al. found that the TDH levels increased in the oxidation direction. In our study, unlike these two studies, we found that the levels of TDH parameters in tinnitus patients are indistinguishable from those in the control group. Therefore, we think that studies on TDH with larger series of patients with tinnitus are needed. In our study, unlike these two studies, IMA and IMA/AlbR levels were also studied, and IMA/AlbR levels were found to be significantly higher in the tinnitus group. It was found that the cut-off value of 14.29 could be used for IMA/AlbR in the ROC analysis in the sample group (AUC: 0.676, sensitivity: 96%, specificity: 32.5%). As it is a subjective symptom, it is difficult to use an objective biochemical test in the etiological diagnosis of tinnitus in terms of ischemia. However, the development of an objective diagnostic test is extremely important. Therefore, the usability of the proposed IMA/AlbR should be improved by standardizing it and working in larger series.

There are critical roles of TDH in the cell such as antioxidant defense, detoxification, regulation of enzyme activities, tran-

scription, apoptosis, and signal transduction mechanisms. Only a very small portion of the plasma thiol pool has low molecular weight thiols such as cysteine, homocysteine, and glutathione. Oxidant molecules oxidize the thiol groups of the cysteine residues in these proteins and convert them into reversible disulfide bond structures. These disulfide bond complexes can be further cut down to thiol groups and therefore the TDH is maintained. As can be understood from this mechanism, the most important protein on the basis of TDH is albumin, which is the most abundant protein in the plasma. Thus, all types of changes occurring in albumin affect the plasma TDH. In the present study, an increase was found in IMA levels in tinnitus patients, but no difference was observed between tinnitus patients and controls in terms of TDH. This condition may suggest that there is a change in albumin, which is the predominant protein in plasma, but the TDH is still compensated, and TDH may also change in the later stages. This opinion is supported by the fact that albumin had a strong positive correlation with TT and NT, while IMA and IMA/AlbR had a strong negative correlation with them.

The fact that treatments that correct the level of ischemia in tinnitus are partially successful in tinnitus in previous studies and that finding higher IMA and IMA/AlbR levels in patients with tinnitus in our study suggests that ischemia is one of the important factors in the etiology of tinnitus. This issue should be studied in larger series.

Limitations of the study

Since the current study is single-centered, the number of participants is partially limited.

Conflict of Interest: The authors declare that there is no conflict of interest.

Ethics Committee Approval: The study was approved by the KTO Karatay University Faculty of Medicine Pharmacological Non-Medical Research Ethics Committee (No: 2018/011 Date: 24/10/2018).

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