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# Audiometry and biochemical analysis in patients with tinnitus — preliminary findings

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## ABSTRACT

**Introduction:** Tinnitus is a sound experience despite the lack of acoustic stimuli in the environment. This study aimed to report the audiometry and biochemical analysis of patients with tinnitus compared with the reference group.

**Material and methods:** The study included a total of 26 patients aged from 20 to 72 years with diagnosed idiopathic tinnitus and 19 healthy subjects as a control group. All patients underwent audiometric tone test, speech audiometry, distortion otoacoustic emissions product testing, the study of evoked auditory potentials of short latency, and biochemical analysis of venous blood concerning values of activity or concentration of the selected parameters of oxidative stress.

**Results:** Mean values of activity or concentration of the selected parameters of oxidative stress in the study and control groups showed reduced effectiveness of the body's natural antioxidant barrier and intensification of treatment of lipid peroxidation. Discussion: There are a lot of factors suspected to generate tinnitus. A lot of them seem to be connected with biochemical disturbances inside the cochlea and in the central nervous system. It will be helpful to set such a battery of tests that contains the predictive indicators of tinnitus. It will be best if it is the battery of standard, not expensive tests of blood.

**Conclusions:** Proper levels of antioxidants may protect hearing. Glutathione and antioxidative enzymes may protect hearing organs against damage caused by free radicals. A lower level of the antioxidants and associated intensification of lipids peroxidation processes may increase free radicals-associated damage and lead to hearing organ dysfunction.

**Key words:** tinnitus, oxidative stress, antioxidant barrier, hearing, audiometry

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## Introduction

Tinnitus is a sound experience despite the lack of acoustic stimuli in the environment. The relationship between hearing deficits and tinnitus is not clear. A few chronic tinnitus patients show normal hearing thresholds in the pure tone audiometry from 125 Hz to 8000 Hz ( $\leq 20$  dB) [1–5]. Such heterogeneity of tinnitus constitutes a major challenge for clinical studies — the aetiology of tinnitus covers the complex interaction of many factors.

This study aimed to report the audiometry and biochemical analysis, with particular emphasis on selected parameters of oxidative stress, of those patients with tinnitus compared with the reference group.

## Material and methods

The study included a total of 26 patients aged from 20 to 72 years (mean age: 54.19 years) with tinnitus, who were diagnosed with tinnitus in the Department of Otolaryngology and Otolaryngological Oncology Unit with the Subunit of Audiology and Phoniatics of Nicolaus Copernicus University *Collegium Medicum* in Bydgoszcz.

The control group consisted of 19 healthy subjects (recruited among acquaintances) aged 20 to 60 years (mean age 49.2), who were not complaining of any audiological problems, well communicating by hearing, not receiving any chronic medication (Tab. 1).

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**Table 1.** Patients overall profile

	<b>Study group n = 26 (100%)</b>	<b>Reference group n = 19 (100%)</b>
Age [years]:		
Min	20	20
Max	72	60
Mean	54.19	49.2
Gender:		
F	14 (53.85%)	10 (52.63%)
M	12 (46.15%)	9 (47.37%)

of Biochemistry of Nicolaus Copernicus University *Collegium Medicum* in Bydgoszcz. Tests were carried out on the same day, within approx. 1 hour of material collection. Based on own studies, no statistically significant differences in haematocrit between the study and the control group were noted. From the blood drawn into tubes without anticoagulant (approx. 3 ml) serum was obtained by centrifugation of the material over 5 min at 5000 × g, then it was transferred to Eppendorf tubes and frozen at -80°C. The prepared serum was stored

**Table 2.** Tinnitus characteristics and influence on speech understanding

	<b>Min</b>	<b>Max</b>	<b>Mean</b>	<b>SD</b>	<b>Median</b>	<b>Q1</b>	<b>Q2</b>
Intensity	10	110	58.2	22,54	60	40	75
Frequency	500	8000	3370	1869,6	4000	2000	4000
Localization	L: 12 patients (46,15%), R: 8 patients (13,77%), L,R 6 patients (23.08%)						
Annoyance	2	10	6.69	2.24	7	5.25	8
Psychological effect	Concentration: 15 patients (57.69%), irritability: 7 patients (26.92%), sleep: 3 patients (11.54), heaviness: 1 patient (3.85)						
Camouflage	Present: 9 patients (40.9%), absent: 13 patients (59.1%)						
Time characteristics	Continuous: 20 patients (76.92%), throbbing: 6 patients (23.08%)						
<b>Speech audiometry (R ear)</b>							
Threshold of distinction	20	80	33.57	17.33	30	20	40
Level of distinction	100% has 100%						
<b>Speech audiometry (L ear)</b>							
Threshold of distinction	10	90	45.71	26.23	40	25	70
Level of distinction	100% has 100%						

Cut-off level (R) 47.92, f = 8000 Hz; cut-off level (L): 63.33, f= 6000 Hz

The results of anamnesis and tinnitus effect on the ability for speech understanding are summarized in Table 2.

Mean hearing loss in the study patients on tonal audiometry was: 30,6dB (SD = 24, 81, median 25) in the left ear and 44,8 dB (SD = 27, 82, median 38, 57) in the right ear, taking into consideration frequencies from 125 to 8000Hz.

All patients underwent the tone audiometric test (audiometer Interacoustic), speech audiometry (audiometer Interacoustic), distortion otoacoustic emissions product testing (camera Madsen) and the study of evoked auditory potentials of short latency – BERA (camera Synapsys).

### Material

The material for analysis was venous blood collected in an amount of approx. 8 ml of the antecubital vein into lithium heparin tubes and tubes without anticoagulant. Blood samples were collected at 8.00. Then, the collected material was transported to the Department

to determine the activity of the oxidase ceruloplasmin (Cp). Before preparing the haemolysate, 500µl blood was collected to determine the levels of glutathione (GSH) in the erythrocytes, the remaining aliquot of blood (approx. 5 ml) was centrifuged to obtain plasma, wherein the concentration of nitrate/nitrite was determined. The remaining cells were used for the preparation of the haemolysate, wherein the dialdehyde malonic concentration (MDA) and the activity of the enzymes: glutathione peroxidase (cGPx), glutathione S-transferase (GST) and superoxide dismutase (SOD-1) were determined.

### Statistical analysis

Where available mean, median, minimum value (Min), maximum value (Max) and standard deviation (SD) were calculated to show the results of this study. The Shapiro-Wilk test was used as a powerful normality test. Parametric t-student test and non-parametric Wilcoxon's test were used to compare scores. Spearman's Rho was used to assess correlations.

All the data in this study were collected and stored using the MS Access 2013 software. Statistical analysis was performed using IBM SPSS Statistics.

The difference was statistically significant at  $p < 0.05$ .

## Ethics

This study was conducted following the Declaration of Helsinki and the guidelines for Good Clinical Practice (GCP). Freely given written informed consent was obtained from every patient before the study.

## Results

No statistically relevant differences between females and males were observed. No statistically relevant

differences between younger and older patients were observed (Tab. 3–7).

Moderate correlations observed in the study group were not observed in the reference group. It may suggest that the distribution of parameters in the study group may reflect the influence of tinnitus (Tab. 8).

## Discussion

Individual or coexisting cochlear (attributed to cochlear impairment) and neural (altered neural firing within the auditory pathway) mechanisms of tinnitus generation may influence auditory temporal resolution in tinnitus patients even with normal audiometry [2]. The general model of changed hearing thresholds in patients with tinnitus was proposed by Gollnast et al.

**Table 3.** Biochemical parameters (study group)

	Min	Max	Mean	SD	Median	Q1	Q2
HT	33.5	49	41.49	3.19	42	40.25	43
GSH	2.05	3.2	2.58	0.29	2.5	2.36	2.79
GPXOS	172.7	290.3	218.97	29.19	212.1	199.05	240.13
GPXRBC	9.6	18.7	14.33	2.55	14.35	12.89	15.7
GSTRB	2.3	4.4	3.23	0.55	3.1	2.8	3.58
GRRBC1	42	82.8	54.6	10.28	51.7	47.8	58.85
SODRBC1	2050	2770	2411.92	190.07	2380	2312.5	2552.5
MDARBC1	0.23	0.32	0.28	0.02	0.28	0.26	0.29
Nitrates/nitrites	0.46	2.01	1.14	0.42	1.08	0.88	1.44
CP	555.2	1837.6	1078.31	303.89	1008.65	855.95	1192.43
CRP	0.41	6.72	1.67	1.57	0.99	0.58	2.22
Cholesterol	87	345	201.35	58.7	203	161.25	240.25
HDL	36	88	55.31	14.39	52	47.25	61.75
LDL	36	245	125.29	48.36	127	92	150.5
TG	43	248	116.96	49.23	112	82	147.25

**Table 4.** Biochemical parameters (reference group)

	Min	Max	Mean	SD	Median	Q1	Q3
HT	36	48	43.34	3.25	43.75	41.5	45.75
GSH	2	2.6	2.21	0.16	2.175	2.1	2.3
GPXOS	164.2	379.3	246.05	48.29	227.85	220.45	261.55
GPXRBC	14.8	22.2	18.91	2.26	19.4	17.65	20.15
GSTRB	1.7	3.3	2.49	0.42	2.65	2.25	2.7
GRRBC1	37	86	55.15	11.21	54.05	48.75	58.3
SODRBC1	2500	3090	2805.26	184.77	2897.5	2670	2950
MDARBC1	0.19	0.3	0.25	0.03	0.26	0.22	0.28
Nitrates/nitrites	0.09	2.79	0.81	0.63	0.635	0.39	1.03
CP	563.2	2559.4	1340.358	542.45	1271.75	1039.05	1343.15

**Table 5.** Correlations part I (study group)

	HT	GSH	GPXOS	GPXRBC	GSTRB	GRRBC1	SODRBC1	MDARBC1	Nitrates/ nitrites	CP
HT	–	Ns	Ns	Ns	Ns	Ns	Ns	Ns	–0.432 p = 0.028	Ns
GSH		–	Ns	Ns	Ns	0.401 p = 0.042	Ns	Ns	0.39 p = 0.049	Ns
GPXOS			–	Ns	Ns	Ns	Ns	Ns	Ns	Ns
GPXRBC				–	Ns	Ns	Ns	Ns	Ns	Ns
GSTRB					–	Ns	Ns	Ns	0.537 p = 0.004	Ns
GRRBC1						–	Ns	Ns	Ns	Ns
SODRBC1							–	Ns	Ns	Ns
MDARBC1								–	Ns	Ns
Nitrates/ nitrites									–	Ns
CP										–

Ns — not significant

**Table 6.** Correlations part II (study group)

	CRP	Cholesterol	HDL	LDL	TG
CRP	–	Ns	Ns	Ns	Ns
Cholesterol		–	0.452 p = 0.02	0.673 p = 0.000	0.467 p = 0.016
HDL			–	0.414 p = 0.035	Ns
LDL				–	Ns
TG					–

Ns — not significant

**Table 7.** Correlations (reference group)

	HT	GSH	GPXOS	GPXRBC	GSTRB	GRRBC1	SODRBC1	MDARBC1	Nitrates/ nitrites	CP
HT	–	Ns	Ns	Ns	Ns	Ns	Ns	Ns	Ns	Ns
GSH		–	Ns	Ns	Ns	Ns	Ns	Ns	Ns	Ns
GPXOS			–	Ns	Ns	Ns	Ns	Ns	Ns	Ns
GPXRBC				–		Ns	Ns	Ns	Ns	Ns
GSTRB					–	Ns	Ns	Ns	Ns	Ns
GRRBC1						–	–0.587 p = 0.008	0.523 p = 0.022	0.679 p = 0.001	Ns
SODRBC1							–	Ns	–0.596 p = 0.007	Ns
MDARBC1								–	0.557 p = 0.013	Ns
Nitrates/nitrites									–	Ns
CP										–

Ns — not significant

**Table 8.** Correlations (study group)

	HT	GSH	GPXOS	GPXRBC	GSTRB	GRRBC1	SODRBC1	MDARBC1	Nitrates/ /nitrites	CP
Intensity	Ns	Ns	Ns	Ns	Ns	Ns	Ns	Ns	Ns	Ns
Frequency	Ns	Ns	Ns	Ns	Ns	Ns	Ns	Ns	Ns	Ns
Annoyance	Ns	Ns	Ns	Ns	Ns	Ns	Ns	Ns	Ns	Ns
	CR	Cholesterol		HDL	LDL	TG				
Intensity	Ns	Ns		Ns	Ns	Ns				
Frequency	-0.506 p = 0.016	Ns		Ns	Ns	Ns				
Annoyance	Ns	Ns		Ns	Ns	Ns				

Ns — not significant

[4]. Neuronal noise (described by Faisal) may induce changes in the auditory pathway. Many factors such as different age groups and different tinnitus pitches may diminish the results of previous studies [4].

Young patients with tinnitus usually show lower hearing thresholds compared to healthy people of the same age. In adult patients with tinnitus differences may be more heterogeneous: hearing thresholds in patients with tinnitus are lower in low-frequency ranges, while they are higher at high frequencies [4]. Transient evoked otoacoustic emissions (TEOAE) and ultra-high frequency (UHF) hearing thresholds may be severely influenced in patients with tinnitus: TEOAE are abnormal in 72.2% of the tinnitus patients, and 18.2% of the control group and UHF thresholds are poorer [5].

There are a lot of factors suspected to generate tinnitus. A lot of them seem to be connected with biochemical disturbances inside the cochlea and in the central nervous system and cause oxidative processes with the activation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) [6, 7]. It will be helpful to set up a set of tests that contains the predictive indicators of tinnitus. It will be best if it is a set of inexpensive blood tests. Direct measurement of oxidative stress may reflect changes in hearing disorders [8]. The aforementioned disorders may be caused by exposition to high-intensity of noise and/or vibrations, the influence of drugs (chemotherapeutics, antibiotics, etc.) resulting in damage of hearing organ structures, loss of hearing, tinnitus or balance disturbances [9–11]. In addition, there is a decrease in the level of antioxidants, which may result in the intensification of lipid peroxidation processes and a decrease in glutathione levels [12–14]. Celik et al. in their studies indicate that the development of oxidative stress and the imbalance of antioxidant enzymes concerns a group of patients with tinnitus [15]. Also, in the authors' other studies, a decrease in the activity of antioxidant enzymes and an intensification of lipid peroxidation processes were

observed in patients with tinnitus compared to the control group. A study by Diao et al. showed that exposition to high-intensity noise may cause to decrease in antioxidative ability in serum and an increase of nitrates in guinea pigs [16], resulting in the generation of toxic peroxynitrite. Increased level of nitrates was observed in patients with tinnitus [17, 18]. Also, in the present study, higher levels of nitrates were observed in the group of patients with tinnitus compared to the control group. An increase in nitric oxide levels may underlie the pathogenesis of tinnitus [18]. Own results showed a correlation between the level of glutathione and the level of nitrates/nitrites. Human glutathione transferase catalyses the formation of S-nitroso glutathione from organic nitrites and glutathione [19]. Increased activity of this enzyme was observed in the present study in patients with tinnitus compared to the control group. In addition, the increase in glutathione levels together with the increase in nitrates supports the protective role of glutathione against the action of free radicals. Also, Koç et al. showed a decrease in antioxidant ability in patients with tinnitus compared with the reference group [20]. Moreover, high-intensity of vibrations may cause hearing damage [21, 22]. Other authors explain the background of idiopathic tinnitus with endothelium dysfunctions and damages of microcirculation within cochlea: the aforementioned situation may intensify processes of lipids peroxidation as far as the increase of concentration of MPO, 4-hydroksynonenal, nitrates or L-arginine [17, 23, 24]. Oxidative processes may lead to disorders of biomechanical paths and tinnitus [25, 26]. Glutathione and antioxidative enzymes may protect hearing organs against damage caused by free radicals. The participation of reactive oxygen species in the development of oxidative stress results in neurootological disorders and may affect the etiopathogenesis of tinnitus.

Tinnitus diagnostics allows for the selection of the treatment method. At least several main ways of treatment

are possible, thus key role plays the precise and objective location of the problem. The main indication to research the functioning of the antioxidant barrier in people suffering from ailments in the form of tinnitus is to determine a suitable therapy aimed at improving the quality of life of these patients, which might be the administration of antioxidant medications. Neurorehabilitation also offers many options: from transcranial magnetic stimulation (TMS) to methods such as McKenzie, OMI Cyriax, etc.

There is a need for further, more detailed studies on bigger samples. Temporal resolution testing in patients with tinnitus may significantly improve diagnosis and therapy [2]. Data-driven categorization of hearing function seems to be a promising approach for profiling tinnitus patients [3].

Further outcomes of the present study will be reported in a more detailed report.

## Conclusions

The proper level of antioxidants may protect hearing. A lower level of the antioxidants and associated intensification of lipids peroxidation processes may increase free radicals-associated damage and lead to hearing organ dysfunction.

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