

# The relation between idiopathic subjective tinnitus and risk factors for venous and arterial thrombosis

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## Abstract

**Aim:** The aim of this study was to investigate the relationship between tinnitus and the factors that cause the tendency to thrombosis in terms of gender.

**Material and Methods:** Fifty-five consecutive patients who admitted to our clinic with the complaint of idiopathic subjective tinnitus were included in this study. Routine ENT (ear nose throat) examinations and pure tone audiometry test were performed. Prothrombin time (PT), partial thromboplastin time (PTT), total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, Triglycerides, antithrombin III (AT III), protein C, protein S, homocysteine, antiphospholipid and anticardiolipin antibodies were examined in blood samples of patients. Temporal bone magnetic resonance imaging (MRI) was performed all patients. The results of the patients were compared in terms of gender and age groups ( $\leq 40$  and  $> 40$  age).

**Results:** The study was completed with 47 patients. Twenty-four of the patients were female and 23 were male. Both genders groups were similar in terms of age and pure tone average. Antiphospholipid and anticardiolipin antibodies (IgG and IgM) were found as negative in all patients. Homocysteine levels were found to be statistically significantly higher in males than females ( $p=0.015$ ; respectively  $13.38 \pm 5.98 \mu\text{mol/L}$  and  $9.87 \pm 3.11 \mu\text{mol/L}$ ). AT III and Protein S levels were lower in males than females although this difference was not statistically significant (respectively  $p=0.07$  and  $p=0.08$ )

**Conclusion:** In this study, an association was shown between hyperhomocysteinemia and tinnitus, especially in males.

**Keywords:** Tinnitus; tinnitus of vascular origin; thrombosis; gender role.

## INTRODUCTION

Tinnitus is defined as the perception of sound in the absence of an external or internal source. More than 50 million people in the United States have reported experiencing tinnitus, resulting in an estimated prevalence of 10% to 15% in adults. It affects markedly negatively the quality of life of approximately 1% of the general population (1,2). Not a disease in and of itself, tinnitus is actually a symptom that can be associated with multiple causes and aggravating cofactors. Despite this high prevalence, only approximately one quarter of adults with tinnitus seek medical help (1-3).

The etiology of tinnitus has not been fully elucidated. Several different factors have been proposed for the etiopathogenesis, some of which have been identified objectively, while most have not been identified, are

accepted as idiopathic or are yet to be explained by theories (2,4). Many parameters can be associated with tinnitus. Some of which are clearly specific like hearing loss, noise exposure, vestibular schwannomas, cerumen, otosclerosis, stress and depression (4,5). However, there are several controversial issues. For example, some of them are role of gender, alcohol consumption, smoking, cerebral stroke, cardiovascular diseases, hypertension, diabetes mellitus and such that (1,5,6).

Numerous acquired and inherited factors are known to cause thrombosis with different mechanisms (67). Venous thrombosis and arterial thrombosis are accepted as two different diseases according to etiologies, pathophysiology, and epidemiology (7,8). Risk factors for thrombosis can be grouped into hereditary (Antithrombin deficiency, protein C deficiency, Protein S deficiency),

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acquired (Antiphospholipid syndrome) and mixed (hyperhomocysteinemia, increased levels of Factor VIII, IX, XI and fibrinogen levels) (7,8). All of the pathologies that contribute thrombosis tendency cause endothelial dysfunction and these situations may affect the feeding of organs (7). The aim of this study was to investigate the relationship between tinnitus and the factors that cause the tendency to thrombosis in terms of gender.

## MATERIAL and METHODS

This study is a prospective study that was performed in accordance with the regulations of the ethics committee of Ankara Atatürk Education and Research Hospital and the declaration of Helsinki. Written informed consent was obtained from all participants prior to the survey. Fifty-five consecutive patients who admitted to our clinic with the complaint of idiopathic subjective tinnitus were enrolled in this study between May 2016 and December 2016. We excluded the following participants: participants who have history of cardiac disease, diabetes mellitus and pulmonary disease; participants less than 18 years of age and more than 65 years of age; participants who have a hearing-loss, participants who has a pathology on magnetic resonance imaging (MRI) and the patients using antithrombotic, antiaggregant therapy. Oral contraceptives drugs were also excluded from the study.

Routine ENT (ear nose throat) examinations and pure tone audiometry test were performed. Then blood samples were taken from patients to investigate the factors causing thrombosis that prothrombin time (PT), partial thromboplastin time (PTT), lipid profile (total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, Triglycerides), antithrombin III (AT III), protein C, protein S, homocysteine, antiphospholipid and anticardiolipin antibodies. Temporal bone magnetic resonance imaging (MRI) was performed all patients in order to evaluate etiology for tinnitus. The results of the patients were compared in terms of gender and age groups. Patients were divided two groups as female and male. Additionally, all patients were divided into two classified as less than 40 years of age and more than 40 years of age.

### Homocysteine measurements

Blood homocysteine levels were measured by "chemiluminescence/magnetic particle" method (Abbott Architect i1000sr immunoassay analyzer, Abbott park, IL 60064 USA).

### Audiological examination

Audiometry tests of the patients were performed using an Orbiter 922 version 2 audiometry device (model EN60645-1; Madsen, Taastrup, Denmark) in the hospital audiology unit. Pure tone air-conduction thresholds were measured in 0.25, 0.5, 1, 2, 4 and 8 kHz frequencies while bone-conduction thresholds were measured in 0.25, 0.5, 1, 2 and 4 kHz frequencies.

### Ethics approval

The study was carried out with the approval of the Clinical

Research Ethics Committee (number 26379996/121).

### Sample size

Inancli et al. have reported that homocysteine levels have high in 39.9% of adult patients with tinnitus (9). The expectation that this rate will change between 20% and 50%, we calculated the minimum number of individuals to be included in the study with 80% power and 0.05 Type I error as 43.

### Statistical analyses

Analysis of the obtained data was performed in the package program SPSS for Windows 11.5 (Chicago, INC. USA). The distribution of each variable in the study was performed by the Shapiro-Wilk's normal test. T test was used for independent samples in comparison of the measured variables by age groups and genders. Two-way ANOVA was used in evaluating the effects of both age groups and gender together, and Ki-Square or Fisher-Exact test (if expected frequencies <5) was used in the evaluation of qualitative variables. The statistical significance limit was accepted as 0.05.

## RESULTS

The study was completed with 47 patients. Six patients who have a vascular loop syndrome and two patients who have a sensorineural hearing loss were excluded. There were 24 female patients with a mean age of  $35.46 \pm 13.24$  years old and 23 male patients with a mean age of  $36.13 \pm 11.95$  years old. Pure tone average was found in the normal range in female and male groups. Both gender groups were similar in terms of age and pure tone average (Table 1). Antiphospholipid and anticardiolipin antibodies (IgG and IgM) were found as negative in all patients.

In the female group, 62.5% of patients were less than 40 years of age, the 37.5% ones were more than 40 years of age while the male group 69.6% of patients were less than 40 years of age, the 30.4% ones were more than 40 years of age. Female and male groups were similar in terms of patients who over the age of 40 and under 40 years (Table 1). While homocysteine levels of plasma in males were average of  $13.38 \pm 5.98$   $\mu\text{mol/L}$ , plasma levels of it in females were  $9.87 \pm 3.11$   $\mu\text{mol/L}$ . In comparison, homocysteine levels were found to be statistically significantly higher in males than females ( $p=0.015$ ). AT III and Protein S levels were lower in males than females although this difference was not statistically significant (respectively  $p=0.07$ ;  $p=0.08$ ) (Table 1). We were not founded the statistically significant difference in terms of other variables such as WBC, HDL, hemoglobin, PT, PTT, Protein C, total cholesterol, LDL and Triglycerides ( $p>0.05$ ; Table 1).

There was no statistically significant difference between  $\leq 40$  and  $>40$  age groups when all these variables were compared according to age groups ( $p>0.05$ ) (Table 2).

When both the age group and gender are evaluated together; AT III was found to be significantly lower in male aged over 40 than female ( $p=0.22$ ); homocysteine was found to be higher in male aged under 40 than females,

although it was not statistically significant ( $p=0.059$ ). Additionally, protein S was detected to be significantly lower in male aged fewer than 40 than female. Nevertheless, this difference was not important statistically ( $p=0.081$ ). When the age and gender effects were evaluated together, it was determined that only total cholesterol was higher in females aged over 40 ( $p=0.044$ ; Table 3).

The most frequently identified pathologies considering the pathological cut-off value were detected in all patients; 17 of patients (38.2%) have high LDL level, 15 patients (31.9%) have low hemoglobin level, 14 of patients (29.8%) have high homocysteine level, and 13 of the patients (27.7%) have low HDL level.

**Table 1. Descriptive values of variables according to gender and their statistical significance results**

	Normal range	Male (n=23) mean±SD	Female (n=24) mean±SD	P
Age		36.13±11.95	35.46±13.24	0.856
Age groups				
<=40		16 (%69.6)	15 (%62.5)	0.609
>40		7 (%30.4)	9 (%37.5)	
PTA (dB)				
Right		13.91±4.94	14.37±4.83	0.747
Left		13.91±4.84	15.21±6.28	0.434
<b>Homocysteine (µmol/L)</b>	0-13	<b>13.38±5.98</b>	<b>9.87±3.11</b>	<b>0.015</b>
AT III* (%)	75-125	98.69±19.81	106.71±7.41	0.070
Protein C (%)	70-140	115.99±12.99	117.98±11.63	0.582
Protein S* (%)	60-130	73.49±23.28	86.36±25.85	0.080
PT (sec)	8.8-14	11.85±0.62	11.65±0.57	0.239
PTT (sec)	22-34	26.51±4.56	24.72±3.11	0.122
WBC (×10 <sup>9</sup> /l)	4-11	7.24±2.02	6.97±1.41	0.600
HDL (mg/dL)	35-55	44.96±16.17	48.52±12.95	0.408
LDL (mg/dL)	0-130	119.35±33.07	113.16±40.68	0.571
Triglycerides (mg/dL)	0-200	153.13±76.21	122.21±67.22	0.147
Hemoglobin (g/dL)	13.5-18	14.54±1.61	13.75±2.07	0.149
Total Kolesterol (mg/dL)	50-200	169.04±29.48	174.54±39.09	0.590

PTA: Pure tone average; AT III: Antithrombin III; PT: prothrombin time; PTT: partial thromboplastin time; WBC: White blood cell; HDL: High-density lipoprotein cholesterol and LDL: Low-density lipoprotein cholesterol. \*:At 3 and Protein S levels were lower in males than females although this difference was not statistically significant

**Table 2. Comparison of Variables by Age Groups (<=40 years, >40 years)**

Variables	<=40 years (n=31) mean±SD	>40 years (n=16) mean±SD	P
PTA (dB)			
Right ear	13.48±5.10	15.44±4.10	
Left ear	14.48±6.11	14.75±4.64	
WBC (×10 <sup>9</sup> /l)	7.02±1.82	7.27±1.53	
HDL (mg/dL)	48.45±14.93	43.53±13.68	
Hemoglobin (g/dL)	14.21±1.97	14.00±1.73	
PT (sec)	11.68±0.46	11.88±0.80	
PTT (sec)	25.05±2.85	26.66±5.45	
At III (%)	103.41±17.13	101.58±10.99	>0.05
Protein C (%)	116.41±11.04	118.17±14.56	
Protein S (%)	76.42±23.83	87.11±27.07	
Total cholesterol (mg/dL)	168.61±25.11	178.13±48.14	
LDL (mg/dL)	118.16±38.73	112.36±33.88	
Triglycerides (mg/dL)	145.32±74.08	121.88±69.52	
Homocysteine (µmol/L)	12.00±5.48	10.79±3.98	

PTA: Pure tone average; WBC: White blood cell; HDL: High-density lipoprotein cholesterol; PT: prothrombin time; PTT: partial thromboplastin time  
LDL: Low-density lipoprotein cholesterol and ATIII: Antithrombin III

**Table 3. The comparison of the descriptive values of variables according to both gender and age groups**

Variables	Age groups	Gender group		p	p (gender*age group interaction)
		Male mean±SD	Female mean±SD		
Right PTA (dB)	<=40	13.87±5.50	13.07±4.80	0.667	0.267
	>40	14.00±3.70 p=0.957	16.56±4.25 p=0.086	0.228	
Left PTA (dB)	<=40	14.00±4.84	15.00±7.37	0.657	0.814
	>40	13.71±5.22 p=0.900	15.56±4.28 p=0.839	0.450	
WBC (×10 <sup>9</sup> /l)	<=40	7.33±2.16	6.68±1.38	0.332	0.327
	>40	7.03±1.78 p=0.750	7.45±1.40 p=0.200	0.600	
HDL (mg/dL)	<=40	45.96±16.17	51.11±13.53	0.345	0.692
	>40	42.67±17.19 p=0.664	44.20±11.32 p=0.213	0.833	
Hemoglobin (g/dL)	<=40	14.69±1.60	13.70±2.25	0.166	0.605
	>40	14.21±1.69 p=0.528	13.83±1.84 p=0.879	0.677	
PT (sec)	<=40	11.70±0.44	11.67±0.50	0.432	0.128
	>40	12.21±0.84 p=0.168	11.62±0.70 p=0.857	0.145	
PTT (sec)	<=40	25.45±1.71	24.62±3.74	0.432	0.176
	>40	28.94±7.68 p=0.277	24.89±1.82 p=0.847	0.145	
At III (%)	<=40	100.43±22.80	106.59±7.17	0.325	0.521
	>40	94.71±10.68 p=0.537	106.91±8.23 p=0.922	0.022	
Protein C (%)	<=40	116.01±12.06	116.83±10.24	0.839	0.690
	>40	115.95±15.97 p=0.992	119.89±14.10 p=0.545	0.608	
Protein S* (%)	<=40	69.19±25.85	116.83±10.24	0.081	0.594
	>40	83.32±12.45 p=0.187	119.89±14.10 p=0.545	0.637	
Total cholesterol (mg/dL)	<=40	173.31±26.57	163.60±23.29	0.289	0.044
	>40	159.29±35.52 p=0.305	192.78±53.35 p=0.076	0.175	
LDL (mg/dL)	<=40	124.10±32.33	111.83±44.84	0.387	0.415
	>40	108.49±34.62 p=0.308	115.38±35.08 p=0.841	0.701	
Triglycerides (mg/dL)	<=40	155.56±76.50	134.40±72.40	0.436	0.587
	>40	147.57±81.32 p=0.823	101.89±55.45 p=0.260	0.202	
Homocysteine* (μmol/L)	<=40	13.79±6.57	10.10±3.24	0.059	0.806
	>40	12.46±4.65 p=0.635	9.50±3.02 p=0.661	0.146	

PTA: Pure tone average; WBC: White blood cell; HDL: High-density lipoprotein cholesterol; PT: prothrombin time; PTT: partial thromboplastin time; LDL: Low-density lipoprotein cholesterol and ATIII: Antithrombin III; \*The difference was not statistically significant

## DISCUSSION

Tinnitus is a common complaint in adults and its pathophysiology has not been explained yet (2,4,10). The arterial or venous thrombosis that may disrupt the blood supply of cochlea may cause tinnitus. There are different ideas about the association between tinnitus and gender. Nondahl et al. reported that the incidence of tinnitus is higher for men than for women (5). In contrast, other

studies have also reported that tinnitus is associated with female gender (10, 11). Therefore, the aim of this study was the investigation of plasma levels of thrombosis tendency factors according to gender in patients with idiopathic subjective tinnitus. The most important finding in our study was the presence of mild hyperhomocysteinemia that a risk factor for thrombosis in male patients. Homocysteine is derived from the metabolic conversion



of the methionine (12). In previous studies is showed that mild-to-moderate hyperhomocysteinemia is associated with increased risk of both arterial and venous thrombosis (12-14). Severe hyperhomocysteinemia (plasma total homocysteine levels greater than 100  $\mu\text{mol/L}$ ) is mostly due to genetic disorders (12, 15). It had been reported that when untreated, the possible rate of exposure to a major vascular event (myocardial infarction, stroke, or venous thromboembolism) before the age of 30 years in these individuals is 50% (13, 15). Mild hyperhomocysteinemia (12-50  $\mu\text{mol/L}$ ) is more common in the community and is a frequent risk factor for stroke, cardiovascular disease and venous thromboembolism (15,16).

Disorder of cobalamin metabolism, deficiency of cystathionine- $\beta$ -synthase and methylenetetrahydrofolate reductase are associated with the hyperhomocysteinemia (12,13). The pathophysiology of arterial and venous thrombosis due to hyperhomocysteinemia is not fully understood. In vivo studies have shown that homocysteine leads to endothelial cell desquamation, smooth muscle cell proliferation, and intimal thickening (12,16). As a result, serious complications as hemiparesis, cor pulmonale depending to pulmonary artery occlusion, severe hypertension owing to renal infarcts, seizures or focal neurological signs because of cerebral thrombosis, and optic atrophy secondary to optic artery occlusion may occur (17).

The mechanism of occurring atherothrombosis due to homocysteine may result from activation of pathways leading to inflammation and apoptosis (15). Hyperhomocysteinemia is a potent inducer of endothelial dysfunction, particularly in small vessels such as cerebral and mesenteric arterioles (15,16). It has been showed that the main vascular pathology in hyperhomocysteinemic animals is endothelial dysfunction, manifested by decreased bioavailability of endothelium-derived nitric oxide (15). The endothelium has an important role in regulating blood flow, coagulation reactions, platelet activation, leukocyte adhesion, and vascular muscle function (15). Endothelial cell molecules as include nitric oxide (NO), prostacyclin, plasminogen activators, and thrombomodulin, are contributed to occurring these reactions. Disruption of endothelial function is shown in experimental models of hyperhomocysteinemia (15).

Inançlı et al. examined tinnitus patients in terms of plasma vitamin B12 and homocysteine levels by grouping them according to whether there were a hearing loss and coexisting disease state. They reported that there was no statistically significant difference in homocysteine and Vitamin B12 levels between the groups (9). In our study, we detected mild hyperhomocysteinemia in male patients as different from female patients.

Ekim et al. reported that hyperhomocysteinemia might be a risk factor for deep vein thrombosis in women over 40 years old (13) In our study, there was no statistically significant difference in homocysteine level between

patients under 40 years of age and older 40 years of age.

Kim et al have reported that tinnitus is associated with female gender, stress, unemployment, noise exposure, hearing loss, hyperlipidemia, osteoarthritis, rheumatoid arthritis, asthma, depression, and thyroid disease history (10). Paulsen et al showed that no relationship between the risk of venous thrombosis and total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, glucose or smoking (6). In previous studies is reported that have been an inverse correlation between HDL levels and the risk for thrombosis. In addition, it has reported that HDL inhibits platelet hyperreactivity by limiting the intraplatelet excess cholesterol load and modulating platelet-signaling pathways after binding to platelet HDL receptors. HDL has antithrombotic features such as the suppression of the coagulation cascade and stimulation of fibrinolysis (18). On the contrary, M. Shirazi et al. reported that the most common type of dyslipidemia is hypercholesterolemia and there is no relationship between tinnitus and dyslipidemia (19). The most frequent findings according to cut off values in our study were following that the increasing of the LDL, homocysteine level and total cholesterol level while low of hemoglobin and HDL level. However, when evaluated according to age and gender, there was no statistically significant association between tinnitus and dyslipidemia.

The protein C, protein S and AT III deficiencies are other risk factors of thrombosis (7). Antithrombin deficiency causes a significant reduction in the inhibition of thrombin and activated factor X and an increase in the tendency of clot formation, especially in the venous system. Activated protein C decreases the rate of thrombin and fibrin formation by inactivates factor Va and factor VIIIa, the two most important activated co-factors of the coagulation cascade. Protein S is a cofactor that increases this inhibitory effect of protein C (7). In our study, although it is not statistically significant in our study, AT III and Protein S levels were lower in males than in females.

One of the important risk factors for thrombosis is Antiphospholipid syndrome. It is characterized by the presence of antiphospholipid antibodies that can lead to arterial or venous thrombosis (7). According to the search we made in PubMed, there is no knowledge about the relationship between Antiphospholipid syndrome and idiopathic subjective tinnitus in the literature. In our study, Antiphospholipid and anticardiolipin antibodies are found negative in both genders.

## CONCLUSION

In this study, an association was shown between hyperhomocysteinemia and tinnitus, especially in males. Further studies are needed to justify the association of tinnitus with peripheral vascular diseases.

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