

ORIGINAL ARTICLE

The Role of Homocysteine in Tinnitus Etiology

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Objectives: The aim of this study is to determine the relationship between homocysteine levels and tinnitus.

Methodology: Ninety-nine patients admitted to our clinic with the complaint of tinnitus between June 2004 and January 2007 were included in our study. The patients were divided into four groups; Group 1 and 2: tinnitus with/without coexisting diseases, Group 3 and 4 tinnitus with/without hearing loss. Group 1 includes patients with tinnitus and coexisting disease, and Group 2 includes patients with tinnitus without any other coexisting disease. Group 3, includes patients with tinnitus and hearing loss and Group 4 includes patients with tinnitus without hearing loss. Plasma homocysteine and vitamin B12 levels were detected and compared among these four groups.

Results: The ages of the 99 subjects were between 19-70 (mean age 49.48 years); 62 were male and 37 female. Of the 99 patients with tinnitus, 43 (43.4%) were in group A, 56 (56.5%) in group B. The most frequent coexisting disease was hypertension, followed by diabetes mellitus and dyslipidemia which was detected by an internal medicine specialist. When group 1 was compared with group 2 and group 3 with group 4, there was no statistically significant difference in the homocysteine and vitamin B12 levels between the groups.

Conclusion: Our study found no statistically significant difference between patient groups in regard to the plasma levels of homocysteine and vitamin B¹². Their role in the etiology and therapy of tinnitus may need further investigation.

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Introduction

Tinnitus can have many different causes. Most common cause of tinnitus is otologic disorders and usually noise-induced hearing loss.^[1] Many theories and etiologic factors have been proposed to explain the mechanisms in the development of tinnitus.^[2-4] A neurovascular theory for tinnitus proposed by Shulman et al led us to investigate homocysteine levels in subjective idiopathic tinnitus (SIT) patients.^[5] There are many studies showing that homocysteine levels are high in patients with vascular diseases such as arteriosclerotic coronary heart disorders, cerebrovascular diseases and low extremity occlusive disorders.^[6] It is also argued that homocysteine has direct neurotoxic effects and may be a risk factor for

cerebral microvascular disease.^[7-10] As it is known that vascular reasons may also contribute to the pathogenesis of tinnitus, we planned to investigate the plasma levels of homocysteine in patients with SIT.

Materials and Methods

The study was performed in a tertiary clinic. Ninety nine patients were enrolled among the patients who admitted to our clinic with the complaint of tinnitus between June 2004- January 2007. All patients fulfilling the study criteria were included. The prerequisite for the study was referral of all the patients with tinnitus as the only complaint. All the subjects were examined by the same internal medicine specialist and the same otolaryngologist. The patients were also checked for temporomandibular joint

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disease, none of them has it.^[11] Gender and social status difference was ignored. The patients were divided into four groups according to the coexistence of other diseases and hearing loss.

Patients with tinnitus additionally either diabetes mellitus, hypertension, dyslipidemia, heart, liver or kidney disease, depression, facial paralysis, thyroid disease, migraine, iron deficiency anemia, tuberculosis, arachnoid cyst, chronic otitis media were included in Group 1 (patients with tinnitus and coexisting disease). The patients in group 1 were evaluated by an internal medicine specialist. Group 2 included the patients with tinnitus without other coexisting disease. Group 3 includes the patients with tinnitus and hearing loss, and group 4 includes the tinnitus patients without hearing loss. The mean values of 500, 1000 and 2000 Hz pure acoustic audiometric test results were taken into account. Hearing loss grading was done according to ANSI (American National Standards Institute) classification using an audiometer (Interacoustic Clinical Audiometer (model AC40; Assens, Denmark).

Plasma homocysteine levels were measured by high-performance liquid chromatography (HPLC) method in plasma, with chromo systems kit, Agilent Technologies 1200 series device (Agilent Technologies, California, USA). As hyperhomocysteinemia is found together with low vitamin B₁₂ plasma levels, vitamin B₁₂ levels (pg/mL,

min: 191pg/mL- max:663pg/mL) were also measured using the same instrument.

The Fisher Exact Test, Pearson Chi Square Test and Independent Sample Test were used for statistical calculations utilizing SPSS program version 15 (IBM SPSS Company, Chicago, Illinois, USA). P<0.05 was accepted as significant p value. The study complied with the declaration of Helsinki and was approved by the local research ethics committee. Ethics committee report had been assigned at 08.02.2007 with approval number of 2007/02/04. All subjects gave informed written consent.

Results

The ages of the 99 subjects included into the study were between 19-70 (mean age 49.48 years); 62 were male and 37 female. Of the 99 patients with tinnitus 43 (43.4%) were in group 1, 56 (56.6%) in group 2, 31 (31.3%) in group 3 and 68 (68.7%) in group 4. Homocysteine levels of groups 1 and 2 were not significantly different from each other. (p>0.05). Even there was not significant difference in terms of homocysteine levels between groups 3 and 4 (p>0.05). The most frequent additional disease was hypertension, the second and the third ones were diabetes mellitus and dyslipidemia respectively. The homocysteine levels of all patients are shown in Table 1. The homocysteine levels of patients in group 1 and 2 are given in Table 2 and group 3 and 4 in Table 3.

Table 1. Homocysteine Levels

	Frequency	%	Valid %	Cumulative %
Normal	51	51,5	51,5	51,5
High	39	39,4	39,4	90,9
Low	9	9,1	9,1	100
Total	99	100	100	100

Table 2. Homocysteine levels of patients in group 1 and 2

			Homocysteine Level			
			Normal	High	Low	Total
Group	Group 1	Number	23	17	3	43
		Ratio(%)	23,2	17,2	3	43,4
	Group 2	Number	28	22	6	56
		Ratio (%)	28,3	22,2	6,1	56,6
Total=n		Number	51	39	9	99
		Ratio(%)	51,5	39,4	9,1	100

Table 3. Homocysteine levels of patients in group 3 and 4

			Homocysteine Level			
			Normal	High	Low	Total
Group	Group 1	Number	19	9	3	31
		Ratio(%)	19,2	9,1	3	31,3
	Group 2	Number	32	30	6	68
		Ratio (%)	32,3	30,3	6,1	68,7
Total=n		Number	51	39	9	99
		Ratio(%)	51,5	39,4	9,1	100

The vitamin B₁₂ levels of the patients in different groups were also investigated. Thirty-nine patients in group 3 (39.4% of 99) had normal levels of vitamin B₁₂, in four subjects (4.0% of 99) vitamin B₁₂ levels were low. In group 2, 53 patients (53.5% of 99) had normal vitamin B₁₂ levels, and in three cases (3.0% of 99) vitamin B₁₂ levels were low. When vitamin B₁₂ levels between group 1 and 2 were compared, there was no statistically significant difference ($p>0.05$). It was found that additional disease in tinnitus had no correlation with vitamin B₁₂ levels.

In group 3 vitamin B₁₂ levels of 29 patients (29.3% of 99) were normal, in two patients (2.0% of 99) vitamin B₁₂ levels were low. In group 4, 63 cases (63.6% of 99) had normal vitamin B₁₂ levels; five cases (5.1% of 99) had low vitamin B₁₂ levels. No statistically significant difference was found between vitamin B₁₂ levels and the existence of hearing loss ($p>0.05$).

Discussion

Tinnitus, one of the most intriguing subjects of otology, is one of the most frequent symptoms encountered in the practice of general otorhinolaryngology and can cause a variety of problems in patients. 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. In patients with tinnitus, cardiovascular, metabolic, neurologic, and psychological diseases are usual.^[12] Diabetes mellitus, hyperinsulinemia, hyperlipidemia, thyroid diseases, vitamin B₁₂ deficiency, and anemia are the most commonly encountered diseases and are thought to play a role in the etiology of tinnitus. In our study, the most frequent disease seen in tinnitus was hypertension. The second and third most frequent

diseases were diabetes mellitus and dyslipidemia. A significant familial effect for tinnitus has also been shown in a recent study.^[13] One of the theories to explain the etiology of tinnitus is the neurovascular theory.^[14] Recent knowledge shows that high blood homocysteine levels are related to ischemic heart diseases, stroke and venous thromboembolic events.^[7, 15-18] Moreover, high homocysteine levels not only are a risk factor for cerebral microvascular disease, it is also reported that they may have direct neurotoxic effects.^[7] Although the exact molecular mechanism of how homocysteine causes arteriothrombotic events is not known, many explanations have been proposed. It is believed that homocysteine can cause thrombogenesis and atherogenesis by endothelial destruction, focal vascular smooth muscle contraction and coagulation abnormalities.^[16] Therefore, as it is known that tendency for vascular pathologies increases in patients with high homocysteine levels, we decided to investigate whether or not homocysteine levels are playing a role in the etiology of tinnitus. However, we found no statistically significant difference between our groups regarding homocysteine levels. Hyperhomocysteinemia, thought of as having a role in all these neural and vascular pathologies. This is usually seen together with low vitamin B₁₂ levels.^[16] Smesh et al^[18] have found a relationship between tinnitus and low vitamin B₁₂ levels and have reported that all patients with tinnitus should be routinely scanned for vitamin B₁₂.^[18] Our study also found no statistically significant difference between groups regarding vitamin B₁₂ levels. We performed this study bearing in mind that high homocysteine levels increase the tendency for neural and vascular pathologies and that hyperhomocysteinemia is often seen together with low vitamin B₁₂ levels and we found no statistically significant relationship between tinnitus and plasma homocysteine and vitamin B₁₂ levels.

Conclusion

Plasma homocysteine and vitamin B₁₂ levels were investigated to support the neurovascular theory of tinnitus, which has not been investigated previously. To our knowledge the relationship between tinnitus and plasma homocysteine and vitamin B₁₂ levels have been not studied before. Although no statistically significant relationship between tinnitus and plasma homocysteine and vitamin B₁₂ levels were found in our study group, we believe that more studies should be performed to support this theory. The effect of homocysteine levels on tinnitus might be more clearly defined if a study could be designed among the patients who have tinnitus and those who don't have tinnitus. High frequency audiometry and ABR are also should be added to the future studies.^[19, 20]

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