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Evaluation of Peripheral Arterial Disease in Patients with Tinnitus Using the Ankle Brachial Index

Tinnituslu Hastalarda Periferik Arter Hastalığının Ayak Bileği Kol İndeksi Kullanılarak Değerlendirilmesi

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ABSTRACT Objective: Tinnitus is sometimes the first manifestation of atherosclerosis. The ankle-brachial index is reported to be a good marker of atherosclerosis and is indicative of peripheral arterial damage. **Material and Methods:** It is a non-invasive test that can be easily applied in the outpatient clinic. We investigated the association of peripheral arterial disease in patients with nonpulsatile tinnitus using the ankle-brachial index. This study demonstrates the role of atherosclerosis in these patients. We evaluated 25 patients who had no hearing loss with nonpulsatile tinnitus and a control group of 15 patients who did not have any tinnitus symptoms. The mean age of all of the patients was 36±12 years. All patients underwent clinical evaluations including a thorough medical and otologic history, micro-otoscopy, complete blood count, clinical biochemical analysis, and pure tone and speech audiometry. Further investigations included magnetic resonance imaging of the internal acoustic canal, and Doppler ultrasound of the carotid and vertebral arteries. **Results:** Patients with an ankle-brachial index <0.9 were accepted as having peripheral arterial occlusive disease. The Mann-Whitney U test showed that the ankle-brachial index was significantly lower in patients with tinnitus (p=0.02). **Conclusion:** This study shows that peripheral arterial disease is more common in patients with nonpulsatile tinnitus than in controls without tinnitus. Our findings support the view that atherosclerosis plays an important role in the cause of nonpulsatile tinnitus.

Keywords: Tinnutus; atherosclerosis; carotid artery disease; ankle-brachial index

ÖZET Amaç: Tinnitus bazen aterosklerozun ilk belirtisidir. Ayak bileği-kol indeksinin aterosklerozun iyi bir belirteci olduğu ve periferik arter hasarının göstergesi olduğu bildirilmektedir. **Gereç ve Yöntemler:** Poliklinikte rahatlıkla uygulanabilen noninvaziv bir testtir. Ayak bileği-kol indeksini kullanarak nonpulsatil tinnituslu hastalarda, periferik arter hastalığı ilişkisini araştırdık. Bu çalışma, bu hastalarda aterosklerozun rolünü göstermektedir. Nonpulsatil tinnituslu işitme kaybı olmayan 25 hastayı ve tinnitus semptomu olmayan 15 kontrol grubunu değerlendirdik. Tüm hastaların yaş ortalaması 36±12 yıl idi. Tüm hastalara kapsamlı bir tıbbi ve otolojik öykü, mikro-otoskopi, tam kan sayımı, klinik biyokimyasal analiz, saf ses ve konuşma odyometrisi dâhil klinik değerlendirmeler yapıldı. Daha ileri araştırmalar, dahili akustik kanalın manyetik rezonans görüntülemesini, karotis ve vertebral arterlerin Doppler ultrasonunu içeriyordu. **Bulgular:** Ayak bileği-kol indeksi <0,9 olan hastaların periferik arter tıkayıcı hastalığı olduğu kabul edildi. Mann-Whitney U testi, kulak çınlaması olan hastalarda ayak bileği-kol indeksinin anlamlı olarak daha düşük olduğunu gösterdi (p=0,02). **Sonuç:** Bu çalışma, periferik arter hastalığının, nonpulsatil tinnituslu hastalarda tinnitussuz kontrollere göre daha yaygın olduğunu göstermektedir. Bulgularımız, aterosklerozun nonpulsatil tinnitusun nedeninde önemli bir rol oynadığı görüşünü desteklemektedir.

Anahtar Kelimeler: İnnitus; ateroskleroz; karotis arter hastalıkları; ayak bileği-kol indeksi

Tinnitus is the perception of sound when an external stimulus is not present.[1] Its frequency in adults is around 10%, and it has a wide range of effects on quality of life, ranging from minor discomfort to complete impairment.[2] There are a number of differential diagnoses that must be considered in such pa-

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tients, some of which can lead to life-threatening circumstances. The classification of tinnitus is based on its pulsatile or continuous (nonpulsatile) presence and its subjective or objective nature.[3] Subjective, nonpulsatile tinnitus is the most frequent type of tinnitus. Tinnitus can be induced or exacerbated by different conditions and factors, including ototoxicity, stress, excessive noise, infections of the ear or sinus, head and neck injury, and other diseases or conditions such as diabetes mellitus (DM), macro/microangiopathy, arterial hypertension (HT), and disorders of the metabolism.

In many cases, the exact cause is never found. In most cases, tinnitus is thought to be the result of atypical activity in the neural circuitry from the cochlea to the regions of the brain that handle hearing.[4] Various biochemical or inflammatory alterations and oxidative stress have been implicated in the development of problems in the auditory circuitry and auditory symptoms experienced by patients with tinnitus.[5] Most patients with pulsatile tinnitus are found to have risk factors for atherosclerotic disease of the carotid artery, and since the pulsatile form of disease is often caused by vascular pathologies, such patients may be experiencing problems in cochlear micro circulation. In addition, tinnitus and atherosclerosis frequencies are both shown to increase with age.

We considered that atherosclerotic disease may contribute to nonpulsatile tinnitus development, and therefore, sought to investigate the possible role of peripheral artery occlusive disease (PAD) in patients with nonpulsatile tinnitus. PAD is most often the result of occlusion or stenosis in limb arteries as a result of atherosclerotic plaque formation. PAD has a prevalence of five percent at age 60 with a subsequent increase with age.[6] Although PAD generally does present with symptoms, it can occasionally lead to claudication symptoms that worsen with time.[7] The ankle-brachial index (ABI) has long been utilized as an atherosclerosis marker, with values lower than 0.9 shown to be diagnostic for PAD.[8] In fact, patients with possible PAD initially undergo non-invasive testing that includes ABI measurement.[7]

MATERIAL AND METHODS

This study was submitted to the local Ethics Committee of Van Research Hospital on Institutional Research which approved the study design (date: 26.11.2013 no: 2013/4). The study was conducted in accordance with the principles of Helsinki Declaration. All participants provided informed consent. In the study group, 25 patients who were admitted to our ear nose throat clinic at a tertiary health facility with complaints of nonpulsatile tinnitus were followed for 18 months. The time from the onset of tinnitus to admittance to our clinic was a maximum of 1 year. All of the patients had nonpulsatile tinnitus. Fifteen people were included in the control group and they were selected from patients who applied to our ear nose throat clinic with complaints other than ear disease.

All patients underwent clinical evaluations including a thorough medical and otologic history, micro-otoscopy, complete blood count, biochemical measurements, and pure tone and speech audiometry. Further investigations included magnetic resonance imaging (MRI) of the internal acoustic canal, and Doppler ultrasound of the carotid and vertebral arteries. Blood samples were also analyzed with regard to the hemogram, glucose, urea, creatinine, thyroid function tests (TFT), triglyceride, cholesterol, aspartate aminotransferase, and alanine aminotransferase. Study and control patients who had normal results for micro-otoscopy examination, complete blood count, and biochemistry analyses were included. All patients (study and control group) who had normal pure tone audiometry were evaluated and included in the study.

For the calculation of ABI, an ABI-form device (Dopplex D900 audio Doppler; Huntleigh Healthcare Ltd., Cardiff, UK) which used an oscillometric technique to concurrently measure blood pressure in both arms and ankles was used, and the device provided automated results. ABI calculation was performed by dividing the systolic blood pressure of the ankle by the systolic blood pressure of the arm. Patients with an ABI of <0.9 were accepted as having peripheral arterial occlusive disease (PAD).

The Mann-Whitney U test was used to compare the study and control groups. Statistical analyses were performed using SPSS 16.0 for Windows (IBM, United States) and p values of <0.05 were accepted to indicate significance.

RESULTS

The research comprised 25 patients with tinnitus (12 men, 13 women), and 15 control patients (8 men, 7 women). The overall mean age was 36±12 years, ranging from 19 to 49 years. Eight patients had tinnitus in the left ear, seven patients had it in the right ear, and 10 patients had bilateral tinnitus. None of the patients in the study group were diagnosed with DM, while three had HT and 11 were smokers. No subjects had DM or HT in the control group, while 6 were smokers. Participants in the study and control groups had normal values of hemogram, cholesterol, and TFT. Carotid arterial and vertebral arterial Doppler ultrasonography investigations did not reveal prominent plaque formation, stenosis, or occlusion. The common/internal/external carotid artery (CCA, ICA, ECA) calibrations and their blood-flow (direction, properties) were visualized and evaluations showed that these features were normal. MRI of the ear did not reveal any pathological signs in any patient.

All patients in the control group had an ABI>1. The ABI differed statistically significantly between the patients with and without tinnitus, i.e. the study and control group (p=0.02) (Figure 1, Table 1). The ABI was significantly lower in the patients with tinnitus, and this was taken to indicate that they had peripheral arterial occlusive disease (PAD).

DISCUSSION

The inner ear is considered to be a sensory neural organ that is sensitive to systematic pathology such as cardio-metabolic, autoimmune, or inflammatory conditions.[9] Tinnitus results from damage to the cochlea's hearing sensory cells, with or without concurrent damage to central auditory system components, due to a variety of factors.[10] Exposure to loud, hearing impairment, aging, DM, HT and middle ear infection are associated with its development.[11] Tinnitus may also be a condition that manifests as the initial symptom of atherosclerosis.[12,13] Various triggering events may be responsible, including microcirculation dysfunction in the inner ear (related to atherosclerotic carotid artery disease) or turbulent blood flow in the carotid arteries.[14,15] However, the precise etiology is yet to be determined.

Although peripheral arterial disease is a disease that presents substantial healthcare burden and is an independent risk factor for cardiovascular mortality and systemic atherosclerosis, it often cannot be identified until advanced symptoms appear. When evaluating patients for PAD, proper diagnostic tools are just as crucial as clinical knowledge and competence. Nowadays, for the diagnosis of PAD, the ABI has become an important tool. Lower ABI values have been associated with generalized atherosclerosis, as a result of studies investigating CCA intima-media thick-

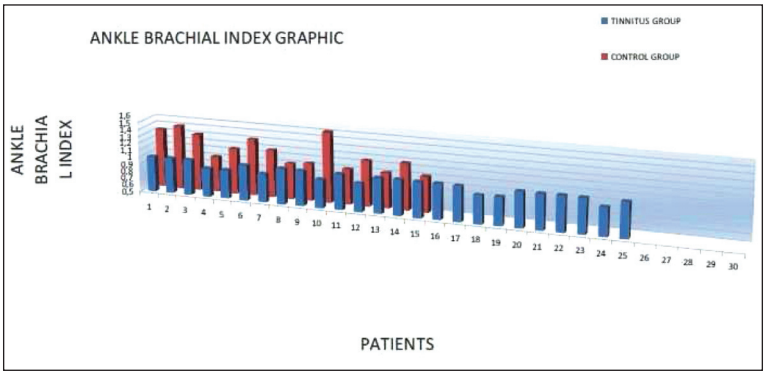

FIGURE 1: Graphic of ankle-brachial index for each patient with tinnitus and controls without.

TABLE 1: Ankle brachial index in patients with tinnitus and controls without tinnitus.

	Patients with tinnitus (n=25)	Control group (n=15)	p value
Ankle-brachial index (mean±SD)	0.96±0.04	1.12±0.16	0.02

SD: Standard deviation.

ness (IMT) and stenosis in the intracranial ICA and middle cerebral artery.[16,17]

Arterio-arterial anastomoses, arteriovenous shunts, and intraluminal irregularities of the carotid system (carotid atherosclerosis, atherosclerotic carotid stenosis, and fibromuscular dysplasia), aberrant carotid artery, middle ear vascular neoplasms, and heart murmurs are all factors associated with pulsatile tinnitus.[18] Atherosclerotic carotid artery disease causes pulsatile tinnitus.[11]

IMT values are extensively used as markers of atherosclerosis.[10] In individuals with pulsatile tinnitus, higher IMT was suggested to represent intracranial arterial sclerosis according to Fukatsu et al. They found significantly elevated IMT values in patients with pulsatile tinnitus compared to those without.[19] Terzi et al. also reported similar findings.[20] Wada et al. evaluated the IMT of the carotid artery in patients with benign paroxysmal positional vertigo, and found it thicker. Thus, they demonstrated that atherosclerosis is more extensive in peripheral vestibular diseases.[21]

We investigated patients with nonpulsatile tinnitus using MRI of the ear, and carotid and vertebral arterial Doppler visualization and we did not detect any pathology. We did not measure IMT but we did not note a higher degree of intimal thickness or plaque formation in the carotid Doppler study. So atherosclerotic signs were not present in the carotid artery in our study. In reported studies, carotid atherosclerosis and atherosclerotic carotid stenosis commonly lead to pulsatile tinnitus.[19,20] In our patients, extensive atherosclerosis was present in the peripheral arteries apart from the carotid artery, which may be related that atherosclerosis is present in patients with nonpulsatile tinnitus but it exists in different locations.

In our study, all causes that may lead to tinnitus were excluded (by hemogram, extensive biochemical analysis, and abnormal signs in MRI, carotid Doppler, and vertebral arterial Doppler, audiogram), and the presence of peripheral arterial disease was investigated in these patients by considering that atherosclerosis might play a role in the etiology of tinnitus. Our results revealed a higher frequency of peripheral arterial disease in patients with nonpulsatile tinnitus. This supports the view that atherosclerosis is a risk factor in nonpulsatile tinnitus.

Nondahl et al. found that, among the cardiovascular-related risk factors, peripheral vascular disease was associated with tinnitus.[10] Recent research has examined hearing impairment as a sign of circulatory instability.[9] Tan et al. found that a history of cardiovascular disease (CVD) and almost all modifiable CVD factors were associated with hearing loss.[22] The presence of tinnitus without hearing loss in a patient may indicate the initiation of cellular damage that has not yet reached a level to produce loss of hearing. The present study demonstrates that atherosclerosis had actually begun to develop in those patients experiencing tinnitus but was present together with normal results for all analyses including audiometry. In our study, a duration of tinnitus for less than 1 year in all patients, and normal results for all parameters apart from the ABI, support the view that tinnitus is an early manifestation of atherosclerosis.

We selected patients with a normal microscopic ear examination and who did not have hearing loss, and whose results of the hemogram, biochemical analysis, and MRI of the ear were normal; however, we did not exclude HT and smoking which can be causes of tinnitus. Therefore, all the other risk factors that might cause tinnitus have been excluded apart from these 2 factors.

CONCLUSION

In conclusion, this study shows that PAD has higher frequency among individuals with tinnitus. There-

fore, it is possible to speculate that atherosclerosis might play a significant role in the etiology of non-pulsatile tinnitus. Additionally, tinnitus may be an early marker for CVD and for that reason, further studies are needed.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Sermin Kibar Şayan, Ayça Özbal Koç;* ***Design:*** *Sermin Kibar Şayan, Ayça Özbal Koç;* ***Control/Supervision:*** *Sermin Kibar Şayan;* ***Data Collection and/or Processing:*** *Sermin Kibar Şayan, Ayça Özbal Koç, Emre Özker;* ***Analysis and/or Interpretation:*** *Sermin Kibar Şayan, Ayça Özbal Koç, Görkem Kanar, Emre Özker;* ***Literature Review:*** *Sermin Kibar Şayan, Ayça Özbal Koç, Görkem Kanar, Emre Özker;* ***Writing the Article:*** *Sermin Kibar Şayan, Ayça Özbal Koç;* ***Critical Review:*** *Emre Özker, Görkem Kanar;* ***References and Fundings:*** *Sermin Kibar Şayan, Ayça Özbal Koç, Emre Özker, Görkem Kanar;* ***Materials:*** *Sermin Kibar Şayan, Ayça Özbal Koç, Görkem Kanar, Emre Özker.*

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