Evaluation of aortic stiffness by echocardiography in tympanosclerosis patients

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Background and Aims. Tympanosclerosis (TS) is a scarring process that may occur during otitis media. Aortic stiffness (AS) is a significant predictor for the development of heart diseases due to its close relationship with atherosclerosis. Similar pathophysiological processes based on inflammation may explain both TS and AS formation. This study aimed to determine echocardiographically whether aortic elasticity is impaired in TS-detected patients and to correlate blood inflammatory parameters with TS and aortic elasticity.

Methods. Ninety-eight participants diagnosed with chronic otitis media were enrolled in the study. TS-detected 42 participants were assigned to the study group, while 56 without TS constituted the control group. The two groups' demographic, clinical, echocardiographic, and laboratory characteristics were comparable.

Results. Demographic, clinical, and laboratory parameter differences were insignificant. Hs-CRP, neutrophil-to-lymphocyte ratio, and systemic immune-inflammation index were significantly higher in the study group than in the control group (P=0.018, P=0.003, P=0.019, respectively).

The study group had significantly lower aortic strain (11.80 ± 4.84 vs. 16.30 ± 3.91; P<0.001) and distensibility (5.23 ± 2.68 vs. 7.24 ± 2.89; P=0.001) values than the control group. The AS index was significantly higher in the study group than in the control group (4.81 ± 2.41 vs. 3.12 ± 1.02; P<0.001).

Conclusion. In TS-detected patients, AS parameters were found to be impaired. Aortic elasticity parameters measured by echocardiography, a non-invasive and easily accessible method, may signify early cardiovascular involvement in TS-developed patients.

Key words: aortic stiffness, tympanosclerosis, inflammation, echocardiography

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INTRODUCTION

Tympanosclerosis (TS) is a scarring process that may occur during otitis media. It manifests primarily with calcified hyaline plaques in different localizations, such as the middle ear and eardrum. Clinically, white plaques may be present at a specific site or may surround the manubrium mallei in the form of a horseshoe[1-3]. The prevalence of TS has been reported to be approximately 10% (ref.[4,5]). Autoimmunity, genetic predisposition, injury and infections have been suggested as potential etiologic causes of TS (ref.[6,7]). Regardless of etiological factors, the inflammatory process triggers reactive oxygen species (ROS) overproduction. Previous studies have shown that tissue damage due to ROS insult occurs in many diseases such as cataract, cerebrovascular disease, atherosclerosis, arthritis. In TS etiopathogenesis, ROS-induced oxidative stress causes tissue damage and the deposition of calcified plaques in the fibrous layer of the eardrum[8-10].

Aortic stiffness (AS) is a well-known predictor for the development of atherosclerosis and related diseases[11]. Loss of aortic wall elasticity due to mechanical stress is considered the main cause of AS formation. Increased migration of inflammatory cells such as mononuclear lymphocytes, high activity of matrix metalloproteinases, cytokines and cell adhesion molecules in the arterial wall are the endogenous causes that accelerate oxidative stress and subsequently the formation of AS (ref.[12]). Similar pathophysiological processes based on inflammation may explain both TS and AS formation. However, no studies have investigated the relationship between AS and TS. We hypothesized that aortic elasticity might be impaired in patients suffering from TS. The current study aimed to evaluate the aortic elasticity properties by echocardiography in TS-detected patients.

MATERIALS AND METHODS

Patients attending the otolaryngology outpatient clinic between 2018 and 2021 with chronic otitis media were eligible for the current study. The participants with insufficient echocardiographic image quality, known coronary or peripheral artery disease, left ventricular (LV) systolic impairment, acute coronary syndrome, severe valvular disease, congenital heart disease, cerebrovascular disease, arrhythmia, liver or kidney failure, malignancies, accompanying endocrinological disorders, chronic inflammatory disorders, anti-inflammatory drug or antibiotic use were excluded. Patients presenting with angina or similar

symptoms in the eligibility evaluation and patients with noninvasive test results suggestive of ischemia were also excluded. According to these criteria, 128 patients were evaluated and 98 patients were eligible for the research. Participants were allocated to two groups and 42 of them that met the criteria were found to have TS. The diagnosis of TS was made from hyaline plaques in the middle ear, tympanic membrane, sclerotic foci, or TS detected in the mastoid cavity during surgery. In cases of spontaneous perforation of the eardrum in non-operative patients, detection of middle ear sclerosis on otoscopy was accepted as a diagnostic criterion. The control group comprised 56 patients who did not have hyaline plaques in the middle ear's tympanic membrane remnant or tympanosclerotic foci. Patients with tympanic membrane perforation in the mastoid and without hyalinization during surgery were also included in the study.

Demographic and clinical data

A detailed anamnesis was taken from all participants, and physical examinations were performed. Demographic and clinical features were registered, including smoking status, previous illnesses and a family history of cardiovascular disease (CVD). Body mass index (BMI) was measured by using body weight (kg) and height (m) according to the Quetelet index. Before echocardiographic evaluation, each participant's arterial pressures were measured using a mercury sphygmomanometer using the dominant brachial artery.

Echocardiographic assessment

Echocardiographic evaluations were performed with the transthoracic approach in the echocardiography laboratory using the GE Vivid S5 Dimension device (GE Vingmed Ultrasound, Horten, Norway) and the X5-1 (1–5 MHz) probe with simultaneous electrocardiography (ECG) monitoring. All measurements were made in three consecutive beats and averaged. The ascending aorta diameters were measured at the end of the systole and the diastole from the parasternal long-axis window using M-mode. Approximately 30 mm distal to the aortic valve, the interspace between the interior border of the anterior and posterior aortic walls was measured and recorded. We measured the aortic end-systolic diameter (AoS) when the aortic valve was entirely open. The aortic end-diastolic diameter (AoD) was measured simultaneously with ECG at the peak of the QRS complex.

The AS calculation was made using the formulas given below:

- Aortic strain (%) = 100 × (AoS − AoD) / AoD
- Aortic distensibility (cm2.dyn-1.10-6) = 2 × aortic strain / pulse pressure
- Aortic stiffness index (beta index) = log (systolic pressure / diastolic pressure) / aortic strain

Laboratory assessment

Blood specimens were collected after 12 h of fasting by inducing mild venous stasis in the upper arm. The samples were placed in potassium ethylenediamine tetraacetic acid tubes for blood counts. Hemoglobin levels, white blood cells and platelet counts were determined with an automatic blood count device (Coulter LH 780, Beckman Coulter) using the electrical impedance method. To calculate the neutrophil-to-lymphocyte ratio (NLR), the total neutrophil count was divided by the lymphocyte count. Systemic immune-inflammation index (SII) was calculated by the formula total platelet count x NLR (ref.[13]) Fasting blood glucose, creatinine, triglyceride, high-density lipoprotein, low-density lipoprotein, and total cholesterol levels were analyzed using standard laboratory methods.

Ethics

All participants signed written informed consent forms. The Local Clinical Research Ethics Committee validated the study protocol and procedures.

Statistical analysis

Data were analyzed using SPSS 17 (SPSS Inc., Chicago, IL, USA) and MedCalc 13.2.0 (Mariakerke, Belgium). Numerical variables conforming to the normal distribution were expressed as means ± standard deviation, numerical variables not conforming to the normal distribution were expressed as medians (interquartile ranges), and categorical variables were expressed as percentages. In the comparison of two independent groups, Student's t-test and the Mann-Whitney U test were used for normal and non-normally distributed continuous variables. A Chi-square test was performed for categorical variables. The cut-off value of the AS index was analyzed by the receiver-operating characteristic (ROC) curve. A value of $P<0.05$ was considered significant.

RESULTS

The median age of the TS (+) group was 63 (41–79), 52.4% were men. The control group median age was 61 (48–75) years, and 46.4% of them were male. Table 1 shows clinical and laboratory features of the TS-developed group patients and control group without TS. There was no statistically significant difference between TS (+) and TS (–) groups in terms of age, gender, smoking status, HT, DM, dyslipidemia, family history of coronary artery disease, BMI and blood pressures. Likewise, hematological and biochemical parameters found to be insignificant.

However, hs-CRP [median 5.3 (2.3–6.3) mg/L vs median 5.0 (2.6–5.6) mg/L, P=0. 018], SII [median 421 (210–803) vs median 348 (139–731), P=0.019], and NLR [median 1.84 (0.78–3.01) vs median 1.61 (0.63–2.18), P=0.003] were significantly higher in the TS(+) group than in the TS(–).

The echocardiographic and aortic elasticity properties of the two groups are shown in Table 2. TS (+) group LV end-diastolic and end-systolic diameters and ejection fraction were close to TS (–). Correspondingly, AoD and AoS values were determined to be insignificant between the TS (+) and TS (–) groups. However, the study group had significantly greater aortic strain (11.80 ± 4.84 vs. 16.30 ± 3.91; $P<0.001$) and distensibility (5.23 ± 2.68

Table 1. Baseline clinical and laboratory characteristics of study and control groups.

Variables	TS (+) (n=42)	TS (–) (n=56)	*P*
Age, years	63 (41–79)	61 (48–75)	0.313
Sex, male n (%)	22 (52.4%)	26 (46.4%)	0.560
Hypertension, n (%)	15 (35.7%)	21 (37.5%)	0.856
DM, n (%)	13 (31.0%)	17 (30.4%)	0.950
Smoking, n (%)	11 (26.2%)	12 (21.4%)	0.582
Dyslipidemia, n (%)	12 (28.6%)	15 (55.6%)	0.845
Family history of CAD, n (%)	8 (19.0%)	8 (14.3%)	0.528
BMI, kg/m^2	26.65 (24.65–27.35)	25.67 (23.10–28.62)	0.219
SBP, mmHg	122.2 ± 13.77	121.1 ± 12.8	0.854
DBP, mmHg	74.5 ± 9.00	73.8 ± 8.60	0.679
Hemoglobin, g/dl	13.61 ± 1.81	14.02 ± 1.28	0.183
White blood cell count, x10^9 /L	7.2 (4.5–9.9)	6.9 (4.8–9.4)	0.829
Platelet count, x10^9 /L	246 (170–377)	236 (143–425)	0.643
NLR	1.84 (0.78–3.01)	1.61 (0.63–2.18)	0.003
hs-CRP, mg/L	5.3 (2.3–6.3)	5.0 (2.6–5.6)	0.018
SII × 10^3	421 (210–803)	348 (139–731)	0.019
Creatinin,mg/dL	0.94 (0.67–1.22)	0.88 (0.69–1.32)	0.486
LDL-cholesterol, mg/dL	118 (79–191)	111 (70–172)	0.620
Glukoz, mg/dL	97 (74–173)	93 (72–184)	0.766
HDL-cholesterol, mg/dL	37 (28–51)	39 (30–57)	0.908
Triglyceride, mg/dL	160 (112–290)	155 (64–359)	0.054
Total cholesterol, mg/dL	191.2 ± 27.23	188.4 ± 28.49	0.630

TS, Tympanosclerosis; BMI, Body mass index; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; LDL, Low-density lipoprotein; HDL, High-density lipoprotein; NLR, Neutrophil-lymphocyte ratio; hs-CRP, high-sensitivity C-reactive protein; SII, Systemic immune-inflammation index.

Table 2. Comparison of echocardiographic and aortic elastic parameters measurements between the study and control groups.

Variables	TS (+) (n=42)	TS (–) (n=56)	*P*
Aortic diastolic diameter (mm)	27.76 ± 4.55	26.34 ± 3.84	0.097
Aortic systolic diameter (mm)	30.88 ± 4.19	30.56 ± 4.04	0.710
LV diastolic diameter (mm)	44.40 ± 1.99	44.91 ± 2.30	0.257
LV systolic diameter (mm)	27.74 ± 2.53	28.16 ± 2.30	0.391
EF (%)	65.0 ± 1.89	65.30 ± 1.48	0.519
Aortic strain (%)	11.80 ± 4.84	16.30 ± 3.91	<001
Distensibility (cm^2.dyne^{-1}.10^{-6})	5.23 ± 2.68	7.24 ± 2.89	0.001
Aortic stiffness index	4.81 ± 2.41	3.12 ± 1.02	<001

LV, Left ventricular; EF, Ejection fraction; TS, Tympanosclerosis.

vs. 7.24 ± 2.89; *P*=0.001) values than the control group. Additionally, the aortic stiffness index was significantly higher in the TS (+) group than TS (–) group (4.81 ± 2.41 vs. 3.12 ± 1.02; *P*<0.001). The ROC analysis revealed a cutoff value of AS index for TS of 3.85, with a sensitivity of 67.1% and a specificity of 75.7% (area under curve, 0.782; 95% CI, 0.640–0.845; *P*<0.001; Fig. 1).

DISCUSSION

The present study examined AS parameters of patients with and without TS by echocardiography. The results showed that patients with TS had lower aortic tension and elasticity values and a higher AS index than those without TS. In addition, inflammatory markers CRP, SII and NLR were significantly higher in patients with TS.

AS association with atherosclerosis and future cardiovascular events is well established[14-16]. Moreover, the results of a previous study encourage the assessment of AS in patients with high cardiovascular risk[17]. The most studied AS formation mechanism involves alteration in the extracellular matrix, uncontrolled proliferation of vascular collagen, a decrease of vascular elastin production and subsequent structural deterioration. In addition, the reduced bioavailability of nitric oxide in impaired endothelium may worsen the condition by inhibiting vasodilation[18]. Endothelial dysfunction and reduced NO bioavailability appear with expected aging, accompanied by inflammation and vasoconstriction, ultimately triggering excessive

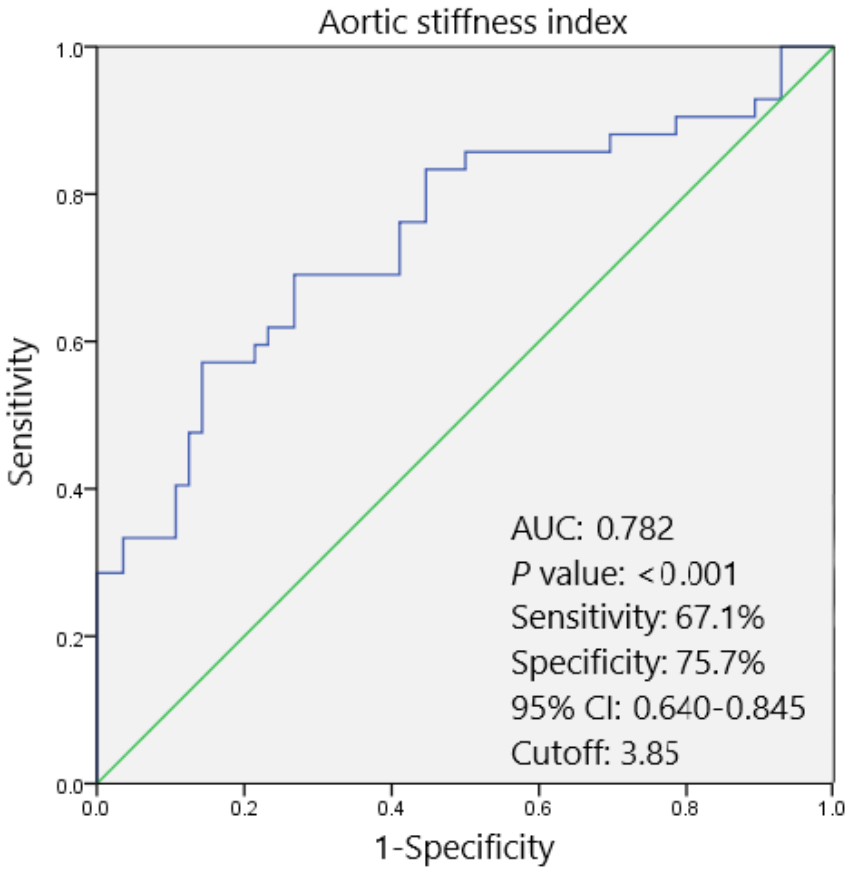

Fig. 1. The receiver-operating characteristic (ROC) curve of aortic stiffness index for predicting tympanosclerosis.

vascular fibrosis and loss of vessel wall elasticity[19,20]. In addition, endothelial dysfunction causes ROS overproduction that accelerates oxidative stress. Eventually, ROS cause changes in hemodynamics by damaging the vessel structures[21]. Increased ROS also takes part in developing AS in atherosclerosis-diagnosed patients. A e paper evaluating peripheral arterial disease found an independent relationship of pulse wave velocity with serum levels of osteopontin and oxidized low-density lipoprotein, which are involved in oxidative stress[22]. These results support the role of oxidative stress in the formation of AS in patients with atherosclerosis.

TS, one of the most common sequelae of otitis media, can present various clinical manifestations, from asymptomatic to severe hearing loss. Previous studies postulated that decreased tissue nitric oxide and catalase levels and subsequently increased ROS production may damage the tissue and play a role in developing TS, as in AS (ref.[19,23]). The development of TS and atherosclerosis may be based on similar predisposition factors and identical pathological processes. Uneri and Koc demonstrated that the ultrastructural appearances of tympanosclerotic and atherosclerotic lesions are similar when examined under light and electron microscopes. Although the etiologies may differ, both diseases have a common reaction in the tissue[24]. Another study reported that the rate of TS was as high as 67% in patients with CVD, while TS frequency in a population without CVD was limited to 12% (ref.[6]). Accordingly, in this study, AS parameters were impaired in patients with TS compared to those without TS, indicating a similar inflammatory process in both entities. The studies showed that aortic wall strain and distensibility decrease and aortic stiffness increases in systemic diseases such as systemic sclerosis, ankylosing spondylitis and metabolic syndrome[25-27]. In the present study, we showed that aortic wall strain and distensibility values might be reduced and also negative progress in the aortic stiffness index may be exhibited in TS-detected patients with more localized inflammatory involvement.

The current study examined hs CRP, NLR, and SII to assess the inflammatory response. NLR is an easily accessible marker that increases systemic inflammation and reflects the risk of future major cardiovascular events[28-31]. It has also been suggested that the newly developed inflammatory marker SII is more valuable than traditional risk factors in predicting cardiovascular events[32]. Additionally, high CRP levels in the circulation are accepted as one of the independent predictors of AS index increase[25]. In the current study, blood serum hs- CRP, NLR and the SII values were found to be much higher in the TS-detected patients than the TS-free patients. Considering the similar inflammatory response in TS and AS, it may be useful to evaluate inflammatory blood parameters in addition to AS in the early detection of cardiovascular involvement in TS-developed patients.

The main limitation of our study is that it was cross-sectional. Since patients were not followed up for cardio-

vascular events, the findings should be supported by larger prospective studies.

CONCLUSION

In conclusion, aortic elasticity parameters measured by echocardiography, a non-invasive and easily accessible tool, were impaired in TS-detected patients. Significant deterioration of AS parameters in TS-developed patients indicates that TS may be a sign of cardiovascular involvement. In addition to the traditional risk assessment, joint evaluation of AS and inflammatory blood parameters in TS-developed patients may guide the detection of cardiac involvement. More studies are needed to understand etiological mechanisms and the association between these two pathologies.

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