Increased carotid artery intima-media thickness in patients with tympanosclerosis: Common risk factors with atherosclerosis?

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KEYWORDS
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Abstract  We investigated the relationship between tympanosclerosis, known atherosclerotic risk factors, and the intima-media thickness of bilateral carotid arteries using ultrasonography. A total of 122 patients admitted to our clinic with chronic otitis media between 2005 and 2010 were included in the study. The study group consisted of 61 patients with tympanosclerosis; the control group comprised 61 patients without tympanosclerosis. Internal carotid artery intima-media thickness (CAIMT), total cholesterol, triglyceride, low- and high-density lipoprotein cholesterol, C-reactive protein, and homocysteine levels were measured in all patients. Homocysteine, low-density lipoprotein, total cholesterol, and triglyceride levels in the study group were higher compared with those of the control group (p < 0.05). Right and left CAIMT was greater in the study group versus the control group (p ≤ 0.001). In conclusion, atherosclerosis and tympanosclerosis were associated with identical risk factors; in the tympanosclerosis group, CAIMT was increased significantly.

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Introduction

Tympanosclerosis (TS) is characterized by hyaline degeneration of the middle ear and mastoid air cells. Although numerous studies have been conducted on TS, its etiology and pathogenesis remain poorly understood. Immunological reactions, genetic predisposition, infection, Helicobacter...
pylori, and trauma have all been proposed as possible etiologic factors [1,2].

A number of etiopathogenetic risk factors have been identified for atherosclerotic vascular disease, of which a positive family history is the most important. Other notable risk factors include lifestyle, smoking, diabetes mellitus, high blood cholesterol and high C-reactive protein (CRP), and homocysteine levels [3,4].

Endothelial dysfunction and increased intima-media thickness in the whole vascular bed represent the most important structural alterations during the early subclinical phase of atherosclerotic disease [5]. Endothelial dysfunction and increased intima-media thickness can be assessed using simple, inexpensive, and noninvasive methods [6] such that therapeutic measures may be used before extensive atherosclerosis develops.

TS incidence is higher in patients with coronary artery atherosclerosis [7–9]. Despite the involvement of different organs, the inflammatory response is similar in both diseases, suggesting a common etiopathogenesis.

We investigate herein the relationship between TS, known atherosclerotic risk factors, and internal carotid artery intima-media thickness (CAIMT).

Methods

The study population consisted of patients admitted to our clinic with chronic otitis media (COM), subsequently divided into two groups according to presence or absence of TS. The study group consisted of 61 patients with TS; TS was diagnosed when hyaline plates were observed on the tympanic membrane remnant or when tympanosclerotic foci were detected in the middle ear and mastoid during surgery. In patients who did not undergo surgery, hyalinization—i.e., a sclerotic appearance in the middle ear on otoscopy in the presence of a tympanic membrane perforation—represented the TS diagnosis criterion. The control group comprised 61 patients without hyaline plates on the tympanic membrane remnant or tympanosclerotic foci in the middle ear and mastoid during surgery, and patients with a tympanic membrane perforation without hyalinization. The exclusion criteria included receiving therapy, or dieting, for hypercholesterolemia, and supplementation with vitamin B12, folic acid, or antioxidants. A total of 122 patients were included in the study. Written informed consent was obtained from all participants, and ethics committee approval was granted.

Total cholesterol, triglyceride, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, CRP, and homocysteine levels were measured in the venous blood samples of all patients after a 12-hour fast. Patients were questioned for family history of myocardial infarction at a young age, and cerebrovascular and obstructive peripheral vascular disease; family history was regarded as positive for atherosclerosis in the presence of at least one of these factors.

All patients underwent ultrasonography using a Logiq 7 (GE Healthcare, Wauwatosa, WI, USA) device, performed by the same radiologist. A 12-MHz, high-resolution linear probe calibrated for the vascular system was used. Gray-scale imaging was performed using the tissue harmonic mode, and Doppler imaging was performed using the color pulse wave method. Vessel diameter and intima-media thickness measurements were obtained at maximum magnification.

The diameter of the common carotid artery was measured 2 cm proximal to the bifurcation, during the diastole. Intimal thickness was measured in the same area, and in two additional areas 1 cm and 2 cm proximal to this location; a total of three measurements were taken, all from the posterior wall of the vessel. Measurements ≤0.9 mm were regarded as normal, and CAIMT >0.9 mm was considered pathological; the location, length, and thickness of plaques were noted in pathological cases. Plaques were classified as fatty, heterogeneous, or fibrous. The presence of calcification, surface characteristics of plaques (i.e., smooth or irregular), and presence of ulcers were recorded.

Data analysis was performed using the SPSS for Windows software package (version 16.0; SPSS Inc., Chicago, IL, USA). Continuous variables were presented as median (minimum—maximum) values, and categorical variables were presented as percentages. Differences in intergroup means were assessed using the Mann—Whitney U test. Chi-square or Fisher’s exact test were used to compare categorical data. A p value <0.05 was taken to indicate statistical significance.

Results

The study group included 30 (49.18%) males and 31 (50.82%) females, and the control group consisted of 26 (42.62%) males and 35 (57.38%) females. The male/female ratios of the two groups were similar (p > 0.05). The median (minimum—maximum) age of the study group was 46 years (range, 13–74 years) versus 39 years (range, 17–63 years) in the control group. The mean ages of the groups did not differ (p = 0.15).

Homocysteine, LDL, and total cholesterol and triglyceride levels in the study group were higher compared with those of the control group (p < 0.05; Table 1). CRP and HDL levels did not differ between groups. In the study group, 32 of 61 (52.5%) patients, compared with 26 of 61 controls, were positive for smoking history (p = 0.27). In total, 38 of 61 patients (62.30%) in the study group, and 28 of 61 controls (45.9%), were characterized by a positive family history (p = 0.069).

CAIMT was higher, on the right and left side, in the study group compared with that found in the control group (both p = 0.0001; Table 2), and there were more plaques in the right and left common carotid arteries of the study group versus the control group (both p = 0.0001; Table 3).

Discussion

TS is an inactive otitis media sequel characterized by hyaline and calcified tissue accumulation beneath the mucosa. Although its etiopathogenesis is unclear, it is known that middle ear infection and tympanic membrane trauma precipitate TS. However, not all patients with middle ear infection, or who have a ventilation tube inserted, develop TS, suggesting that a molecular mechanism with genetic variations may play a role in the development of TS.
Clinical and experimental studies suggest that free oxygen radicals, produced by bacteria and inflammatory cells and appearing in otitis media, play important roles in the development of TS [10,11]. Free oxygen radicals-related tissue injury occurs in a number of conditions including cataract, cerebrovascular disease, atherosclerosis, arthritis, and ischemia–reperfusion injury; tissue injury is necessary for TS to develop.

TS incidence is higher in patients with atherosclerosis [12]. Koç et al (1989) investigated the genetic predisposition for TS and atherosclerosis and compared the TS prevalence between atherosclerotic patients and healthy controls. Otoscopy was performed on 1024 patients with atherosclerosis, of whom 682 (66.6%) patients were positive for myringosclerosis. Myringosclerosis was evident in 36 (12%) of 300 controls (p < 0.0001) [11].

Genetic predisposition is the most important risk factor for the development of coronary artery atherosclerosis. In another study, Koç and Uneri [13] demonstrated that TS was more frequent in males, a trend that has also been reported elsewhere. However, in our study group (31 females and 30 males), both sexes were affected similarly.

Uneri and Koç [7] compared the ultrastructural features of tympanosclerotic and atherosclerotic foci; both lesions were examined under light and electron microscopes, which revealed that their ultrastructural appearances were similar. The authors suggest that these two diseases represent a common reaction in two separate tissues due to different causal factors [7].

Despite the involvement of different organs, the inflammatory reaction is the same in both entities. In a study designed to investigate the co-occurrence of these two diseases, TS prevalence was assessed in a group of patients who had undergone carotid artery surgery for severe atherosclerosis and in age-matched healthy controls. TS was detected in 32 of 84 patients (38.1%) in the study group compared with 11 of 84 controls (13%; p = 0.005) [8]. Right and left CAIMT were significantly greater in the TS group (p < 0.0001), which supports the co-occurrence of these two diseases.

Family history is the most important risk factor for atherosclerosis. In our study, there was a trend toward a higher rate of positive family history in the TS group versus the control group (62.30% and 45.9%, respectively), but this difference was not significant (p = 0.069). We suggest that a significant association between family history and tympanosclerotic middle ear disease might have been observed in the context of a larger sample. Smoking is also an important risk factor for atherosclerosis development [3,4]; smoking was more prevalent in our TS group but not significantly so (p = 0.27).

High LDL levels in the blood are another important risk factor for atherosclerosis [14]. LDL is oxidized by macrophages located in the media layer of middle- and large-

### Table 1 Homocysteine, CRP, LDL, HDL, total cholesterol, and triglyceride levels in the study group and control group.

<table>
<thead>
<tr>
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<th>Study group (n = 61)</th>
<th>Control group (n = 61)</th>
<th>p</th>
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<tr>
<td></td>
<td>Mean ± SD Median Min–Max</td>
<td>Mean ± SD Median Min–Max</td>
<td></td>
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<tr>
<td>Homocysteine (µmol/L)</td>
<td>13.7 ± 7.1 12 2.2–50</td>
<td>10.784 9.87 2.7–33.4</td>
<td>0.003</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>0.74 ± 0.6 0.5 0.3–4.2</td>
<td>0.62 0.5 0.5–2.2</td>
<td>0.055</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>121.8 ± 31.2 122 58–206</td>
<td>107.31 103 65–188</td>
<td>0.006</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>40.5 ± 10.5 37 22–70</td>
<td>42.69 41 24–84</td>
<td>0.385</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>190.1 ± 39.6 193 113–270</td>
<td>170.02 167 104–281</td>
<td>0.001</td>
</tr>
<tr>
<td>Triglyceride (mg/dL)</td>
<td>140.6 ± 92.6 119 26–432</td>
<td>106.07 94 23–282</td>
<td>0.044</td>
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</tbody>
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CRP = C-reactive protein; HDL = high-density lipoprotein; LDL = low-density lipoprotein; SD = standard deviation.

### Table 2 Comparison of carotid artery intima-media thickness between the groups.

<table>
<thead>
<tr>
<th></th>
<th>Study group</th>
<th>Control group</th>
<th>Total</th>
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<tbody>
<tr>
<td></td>
<td>Right</td>
<td>Left</td>
<td>Right</td>
</tr>
<tr>
<td>&gt;0.9 mm</td>
<td>31 (50.82%)</td>
<td>35 (57.37%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>≤0.9 mm</td>
<td>30 (49.18%)</td>
<td>26 (42.63%)</td>
<td>61 (100%)</td>
</tr>
<tr>
<td>Total</td>
<td>61 (100%)</td>
<td>61 (100%)</td>
<td>61 (100%)</td>
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</table>

### Table 3 Comparison of atherosclerotic plaques between the groups.

<table>
<thead>
<tr>
<th></th>
<th>Study group</th>
<th>Control group</th>
<th>Total</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Right</td>
<td>Left</td>
<td>Right</td>
</tr>
<tr>
<td>Present</td>
<td>13 (21.31%)</td>
<td>14 (22.95%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>None</td>
<td>48 (79.69%)</td>
<td>47 (77.05%)</td>
<td>61 (100%)</td>
</tr>
<tr>
<td>Total</td>
<td>61 (100%)</td>
<td>61 (100%)</td>
<td>61 (100%)</td>
</tr>
</tbody>
</table>
sized arteries, which become foam cells resulting in endothelial dysfunction, inflammation, and typical atheroma plaques. These plaques increase the likelihood of bleeding, laceration, and thrombocyte adhesion in these regions [2]. Mean LDL was significantly higher in our study group compared with the control group ($p = 0.006$).

Although less important than high LDL, a high cholesterol level is also a strong risk factor for atherosclerosis [15]. In our study, total cholesterol was higher in the study group ($p = 0.001$), in accordance with the literature.

Recently, CRP, an important marker of atherosclerosis, has been studied extensively. CRP is a biochemical marker of systemic inflammation; high CRP levels are associated with atherosclerosis [16]. Measuring CRP confers significant advantages during the follow up of patients with known atherosclerotic vascular disease [17].

In our study, the mean CRP level was higher in the TS group than in the control group, but not significantly so ($p = 0.055$). We suggest that this finding could reach significance with a larger sample.

Homocysteine is a sulfhydryl-containing amino acid derivative produced following the demethylation of methionine, and present in abundance in animal proteins [18]. High homocysteine levels are observed in atherosclerotic vascular disease patients, who exhibit peripheral vascular and cerebrovascular diseases more frequently than coronary artery disease [19,20]. Another study performed in our clinic demonstrated that homocysteine, in addition to atherosclerosis, is an important risk factor for TS [9]. In accordance with the literature, homocysteine levels were significantly higher in our study group versus the control group ($p = 0.003$). Furthermore, in accordance with previous studies, the absence and presence of pathological CAIMT in the control group, and in a considerable number of patients, respectively, strongly supports the hypothesis that these diseases possess common risk factors.

As mentioned previously, the existence of common risk factors for atherosclerosis and TS suggests that common mechanisms may underlie the development of these two diseases. In support of this hypothesis, well-known risk factors for atherosclerosis such as homocysteine, LDL, total cholesterol, and triglyceride levels were significantly higher in our study group. Pathophysiological studies are required to further delineate the relationship between risk factors and TS.

Studies have typically sought to determine atherosclerotic risk factors so that they may be controlled. However, because atherosclerosis can be simultaneously present in TS patients, a more careful and detailed examination of the cardiovascular system must be performed. In conclusion, we demonstrate herein that atherosclerosis and tympanosclerosis possess identical risk factors; in our tympanosclerosis group, CAIMT was significantly increased. Prospective, randomized controlled studies are required to further delineate the pathophysiological relationship between the risk factors of tympanosclerosis and atherosclerosis.

References