Is there any relation between coronary atherosclerosis and tympanosclerosis?

Koroner ateroskleroz ve timpanoskleroz arasında bir ilişki var mıdır?

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Abstract

Objective: Atherosclerosis is a chronic inflammatory disease of medium and large-sized arteries. Tympanosclerosis is the hyalinization and calcification of the connective tissue in the middle ear, including the tympanic membrane. The etiology and pathogenesis of tympanosclerosis are still controversial. There are some reports about the possible relationship between development of tympanosclerosis and atherosclerosis. Therefore, we aimed a cross-sectional study to investigate relationship between tympanosclerosis and atherosclerosis in patients referred for coronary angiography.

Methods: The study population consisted of 203 consecutive patients (145 men, mean age 59±11years) who underwent coronary angiography. Otoscopic examination was performed in all patients. All angiographies were examined to calculate coronary artery vessel stenosis and extent scores. Mann-Whitney U test was used to compare the angiographic scores with existence of tympanosclerosis.

Results: Among the 203 patients, 35 (17%) patients had angiographically normal coronary arteries without any atheroma plaque and 168 (83%) had coronary atherosclerosis. In the otoscopic examination, tympanosclerosis was found in 14 patients (6.9%). No significant differences in distribution of clinical atherosclerotic risk factors (age, gender, body mass index, hypertension, diabetes mellitus, cigarette smoking and cholesterol levels) were found between groups with and without tympanosclerosis. Tympanosclerosis was found in 4 patients with normal coronary arteries (11.4%). In the group of coronary atherosclerosis, 10 patients have tympanosclerosis (5.9%). In addition, there was no statistically significant association of coronary artery vessel, stenosis or extent scores of atherosclerosis with tympanosclerosis ($p>0.05$).

Conclusions: We could not find any association between tympanosclerosis and angiographic extent and severity of atherosclerosis, contrary to other studies. More studies are needed to understand etiological mechanisms and association between them. *(Anadolu Kardiyol Derg 2010; 10: 121-5)*

Key words: Atherosclerosis, tympanosclerosis, coronary angiography, angiographic scoring

Özet

Amaç: Ateroskleroz orta ve büyük arterlerin kronik inflamatuvar bir hastalığıdır. Timpanoskleroz, timpanik zarı da içine alacak şekilde orta kulak bağ dokusunda hyalinizasyon ve kalsifikasyon oluşmasıdır. Timpanosklerozun etiyoloji ve patogenezi hala tartışmalıdır. Ateroskleroz ve timpanoskleroz gelişimi arasında olası ilişkiye yönelik bazı çalışmalar mevcuttur. Biz bu kesitsel çalışmada, koroner anjiyografiye gönderilen hastalarda timpanoskleroz ve ateroskleroz arasındaki ilişkiyi araştırmayı amaçladık.

Yöntemler: Koroner anjiyografiye gönderilen 203 ardışık hasta (145 erkek, yaş 59±11 yıl) çalışmaya alındı. Bütün hastalara otoskopik muayene yapıldı. Koroner anjiyografilerde damar, darlık ve yaygınlık skorları hesaplandı. Timpanoskleroz varlığı ile anjiyografik skorları karşılaştırmak için Mann-Whitney U testi kullanıldı.

Bulgular: İki yüz üç hastadan, 35 (%17) hastanın anjiyografisi aterom plağı olmadan normal bulunurken, 168 (%83) hastada koroner ateroskleroz tespit edildi. Otoskopik muayenede, 14 (%6.9) hastada timpanoskleroz bulundu. Timpanoskleroz olan ve olmayan hasta grupları arsında klinik aterosklerotik risk faktörleri (yaş, cinsiyet, vücut kitle indeksi, hipertansiyon, diyabetes mellitus, sigara kullanımı, kolesterol seviyeleri) açısından anlamlı farklar tespit edilmedi. Normal koroner arterleri olan hastalardan 4'ünde (%11.4) timpanoskleroz tespit edildi. Koroner ateroskleroz grubunda ise, 10 (%5.9) hastada timpanoskleroz mevcuttu. Ayrıca, timpanoskleroz ile aterosklerozun damar, darlık ve yaygınlık skorları arasında istatistiksel olarak önemli bir ilişki bulunmadı ($p>0.05$).

Sonuç: Diğer çalışmalardan farklı olarak timpanoskleroz ile aterosklerozun anjiyografik yaygınlığı ve ciddiyeti arasında bir ilişki tespit edemedik. Bu iki hastalık arasındaki ilişkiyi ve etiyolojik mekanizmayı anlayabilmek için daha fazla çalışmaya ihtiyaç vardır. *(Anadolu Kardiyol Derg 2010; 10: 121-5)*

Anahtar kelimeler: Ateroskleroz, timpanoskleroz, koroner anjiyografi, anjiyografik skorlama

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Introduction

Atherosclerosis is a multifocal immuno-inflammatory disease of medium and large-sized arteries fuelled by lipids. Endothelial cells, leukocytes and intimal smooth muscle cells are the major players in the development of this disease (1). Chronic inflammation and immune mechanisms are involved in genesis, especially during progression phase and during the onset of vulnerable plaques (2).

Tympanosclerosis is a disease characterized by hyalinization and calcification of the collagen layer in certain areas of the tympanic membrane and middle ear mucosa and appears as white chalky patches (3-5). The exact etiology and pathogenesis of tympanosclerosis is not well known. Some reports have been in agreement that inflammation could initiate formation of the tympanosclerosis (6, 7).

There are some reports about the possible relationship between development of tympanosclerosis and atherosclerosis (8-10). Therefore, in the current study, we aimed a cross-sectional study to examine the relation between tympanosclerosis and angiographic extent and severity of atherosclerosis in patients referred for elective coronary angiography. In addition, we investigated the effect of traditional risk factors on tympanosclerosis.

Methods

The study population consisted of 203 consecutive patients (145 men, mean age 59±11, 27-86 years) who underwent coronary angiography. All of them underwent diagnostic coronary angiography to determine coronary artery disease (CAD) because of typical or quasi-typical symptoms of angina and electrocardiographic changes at the Cardiology Clinic of Mersin University Hospital.

Otoscopic examination

Otoscopic examination was performed bilaterally by a single examiner in order to detect the presence of possible tympanic plaques. Patients with previous otologic disease and otosurgical procedures were excluded. We obtained a verbal informed consent from patients for otoscopic examination. Presence of tympanosclerosis was noted as described by Bluestone in 2003 (11). If at least 20% of the eardrum was occupied with plaques, the case was considered as tympanosclerosis positive. In addition, tympanosclerosis detected in patients was staged as follows:

Stage 1. Tympanosclerosis limited to tympanic membrane and hearing is unaffected;

Stage 2. Tympanosclerosis limited to tympanic membrane, but hearing loss occurs secondary to tympanosclerosis;

Stage 3. Tympanosclerosis involving the middle ear only with no hearing loss;

Stage 4. Tympanosclerosis involving the middle ear with hearing loss;

Stage 5. Tympanosclerosis involving the tympanic membrane and middle ear, with no hearing loss;

Stage 6. Extensive tympanosclerosis involving both the tympanic membrane and middle ear with hearing loss (11).

Risk factors of CAD

The coronary risk profile (blood pressure, diabetes mellitus, smoking status, lipid profile) and current medication were obtained from the patients' records. Diabetes was defined as hyperglycemia requiring previous or ongoing pharmacological therapy. Hypertension was defined as increased systolic or diastolic blood pressure above 140/90 mmHg or ongoing antihypertensive therapy. Body mass index (BMI) was calculated as weight divided by height squared. Smoking was defined as current use of cigarettes >10 cigarettes daily at least for one year. Family history of CAD was considered positive if patient's first- degree relatives had been diagnosed with CAD before 55 years of age.

Biochemical analyses

Total cholesterol, triglycerides and high-density lipoprotein-cholesterol (HDL-C) were analyzed by glycerophosphate oxidase, peroxidase/4-aminophenazone (GPO/PAP), cholesterol oxidase, peroxidase/4-aminophenazone (CHOD/PAP) and direct COHD/PAP enzymatic colorimetric methods, respectively. The content of very low-density lipoprotein-cholesterol (VLDL-C) and low-density lipoprotein-cholesterol (LDL-C) was calculated according to the equation described by Friedewald et al (12). All these parameters were determined by a Cobas Integra 800 biochemical analyzer (Roche Diagnostics, GmbH, Mannheim, Germany).

Coronary angiography

Coronary angiography was applied by femoral approach using standard Judkins technique (13). Coronary angiographies were interpreted visually and were always analyzed in two orthogonal views. Coronary angiograms were independently reviewed by experienced cardiologists blinded to the patients' clinical and laboratory findings. The patients, who had any angiographic evidence of atherosclerosis in their epicardial coronary arteries, including a plaque, were classified as having CAD. The patients who did not have any coronary lesion were classified as without CAD (normal coronary arteries-NCA). All angiographies included in CAD group were examined to determine to the severity of coronary atherosclerosis. The evaluation included three different scoring systems, described by Sullivan et al. (14-16).

Vessel score: Vessel score was 0 to 3 points. Each of the main coronary arterial branches (left anterior descending, left circumflex artery, right coronary artery) having ≥1 stenoses of ≥70% was given 1 point each. If the left main stem, which was regarded as one vessel and the left anterior descending and/or the left circumflex artery were affected, this was counted as 2 points.

Stenosis score: Stenosis score was 0 to 32 points. The maximum diameter reduction of 8 coronary segments (left main stem,

left anterior descending artery, main diagonal branch, main septal branch, left circumflex artery, main marginal branch, right coronary artery, right posterior descending branch) was scored with 1 to 4 points according to a luminal narrowing of 1% to 49% (1 point), 50% to 74% (2 points), 75% to 99% (3 points), or a total occlusion (4 points).

Extent score: Extent score was 0 to 100 points. According to the proportional length of each vessel segment in the coronary artery tree, segments were graded with different maximum numbers of points: 5 points for the left main stem, 20 for the left anterior descending artery, 10 for the main diagonal branch, 5 for the first septal branch, 20 for the left circumflex artery, 10 for the obtuse marginal and posterolateral vessels, 20 for the right coronary artery, and 10 for the right posterior descending branch. The number of points for each segment (irrespective of the degree of diameter reduction) was expressed as the percentage length of visible lesions within the total segment. Occluded vessels that were filled with contrast medium by collateral flow were scored according to the visible irregularities of the vessel wall. If no collateral flow existed, the mean value of all other vessel segments of this angiogram was given to this occluded vessel segment.

Statistical analysis

Statistical analysis was assessed by computer software SPSS for Windows version 11.5 (Chicago, Illinois, USA). All data were presented as mean±SD, median values and proportions/percentages. Differences were considered significant at a value of $p<0.05$.

Analysis of differences in categorical binary variables (gender, hypertension, diabetes mellitus, family history of CAD) between groups with and without tympanosclerosis was accomplished using Chi-square test. Independent samples t test was used to figure out differences between groups in continuous variables (age, total cholesterol, LDL-C, HDL-C, triglycerides, body mass index). Mann-Whitney U test was used to compare the vessel, stenosis and extent scores with existence of tympanosclerosis.

Results

The study population included 203 patients with a mean age of 59±11 years (145 male with mean age of 58±11 years and 58 female with mean age of 61±11 years). Forty-three (21%) patients had diabetes mellitus, 111 (55%) patients had systemic hypertension and 87 (43%) patients had history of cigarette smoking. Forty-three (21%) subjects had a family history of premature CAD.

Otoscopic examination of 203 patients was performed and tympanosclerosis was found in 14 patients (6.9%), it was bilateral in five patients. The involvement degree of tympanosclerosis was stage 1 in all patients. No significant differences in clinical atherosclerotic risk factors (age, gender, body mass index, hypertension, diabetes mellitus, cigarette smoking, family history of CAD, and cholesterol levels) were found between patients with and without tympanosclerosis. The associations of baseline clinical characteristics with presence of tympanosclerosis are presented in Table 1.

Among the 203 patients, 35 patients (17%) have angiographically normal coronary arteries and 168 have coronary atherosclerosis. The prevalence of coronary atherosclerosis was 83%. The 44 (22%) patients had one-vessel disease (>70% stenosis), 44 (22%) patients had two-vessel disease and 41 (20%) had three-vessel disease. The mean vessel score was 1.9±1.4 (range, 0 to 3), mean stenosis score was 5.7±4.4 (range, 0 to 32), and mean extent score was 24.9±16.2 (range, 0 to 100).

Tympanosclerosis was found in 4 out of 35 patients with NCA (11.4%). In the group of coronary atherosclerosis, 10 patients have tympanosclerosis (5.9%). There was no statistically significant differences in vessel, stenosis and extent scores between groups of patients with and without tympanosclerosis ($p>0.05$) (Table 2).

Discussion

We could not found any association between tympanosclerosis and atherosclerosis. With difference of previous studies, we examined also the severity of atherosclerosis and determined vessel, stenosis and extent scores for each patient. However, there were also no statistically significant associations between existence of the tympanosclerosis and the vessel, stenosis or the extent scores.

In the literature, there are two studies about the relation between atherosclerosis and tympanosclerosis (8-10). Koç et al. (8) found a statistical correlation between tympanosclerosis and atherosclerosis. They examined 1024 patients with known CAD and they found an incidence of 67% tympanosclerosis in patients

Table 1. Baseline characteristics of patients with and without tympanosclerosis

Variables	Tympanosclerosis present (n=14)	Tympanosclerosis absent (n=189)	p*
Age, years	59.8±10.9	59.3±11.4	NS
Men, n (%)	11 (79)	134 (71)	NS
Hypertension, n (%)	6 (43)	105 (55)	NS
Diabetes, n (%)	2 (14)	41 (22)	NS
Smoking, n (%)	3 (21)	84 (44)	NS
Family history of CAD, n (%)	1 (7)	42 (22)	NS
Laboratory findings			
Total cholesterol, mg/dl	203.5±59.0	195.9±46.9	NS
LDL cholesterol, mg/dl	133.8±62.5	115.6±37.6	NS
HDL cholesterol, mg/dl	40.0±13.9	46.3±15.1	NS
Triglycerides, mg/dl	178.8±113.1	175.3±103.2	NS
Body mass index, kg/m^2	26.1±3.7	26.5±3.9	NS

Data are presented as mean±SD and proportions/percentages
*- t test for independent samples and Chi-square test
CAD - coronary artery disease, HDL - high-density lipoprotein, LDL - low-density lipoprotein, NS - not significant, p>0.05

Table 2. Results of coronary angiography and the atherosclerosis score of patients with and without tympanosclerosis

Variables	Tympanosclerosis present (n=14)	Tympanosclerosis absent (n=189)	p*
NCA without any atheroma plaque	4	31	NS
Coronary atherosclerosis	10	158	NS
Atherosclerosis scoring			
Vessel score	1.4±0.3 2 (0-3)	1.2±0.1 1 (0-3)	NS
Stenosis score	6.3±1.4 8.5 (0-14)	5.7±0.3 5 (0-19)	NS
Extent score	22.0±4.5 25 (0-45)	25.1±1.2 25 (0-60)	NS

Data are presented as mean±SD, median (min-max) values and proportions
* - Mann Whitney U and Chi-square tests
NCA - normal coronary arteries, NS - not significant, p>0.05

with CAD compared with 12% of the normal population (8). The prevalence of tympanosclerosis in the atherosclerosis group was higher than in our study, but their study criteria were different. Although they had chosen control patients without ear problems, 174 of 1024 patients in the atherosclerosis group had medical histories of ear complaints and infections. In addition, their control subjects were younger than atherosclerotic patients.

Ferri et al. investigated the possible relationship between tympanosclerosis and atherosclerosis in 84 patients with significant carotid disease and presented in two publications (9, 10). They found that patients with carotid atherosclerosis had higher incidence of tympanosclerosis compared to the controls (38 vs 13%, p=0.05; 36 vs 12%, p=0.005).

Major pathophysiological process of coronary atherosclerosis is a defect or injury of the arterial endothelial function and represented by the impairment of blood flow. There is a close link between atherosclerosis and high total cholesterol levels. Also, smoking, high body weight, high blood pressure, elevated fasting glucose and diabetes are important risk factors and the rate of progression of atherosclerosis is highly variable (17, 18). Studies identified that inflammation plays a pivotal role in the onset and progression of atherosclerosis (19, 20). There were no studies on whether these risk factors were associated with tympanosclerosis.

The pathogenesis of tympanosclerosis is unclear. In order to clarify the cause of tympanosclerosis, several hypotheses have been proposed and different scavenging agents were used for prevention (21-24). Otitis media and/or transtympanic tube application are most widely accepted explanations for the genesis of this pathology (7, 25, 26). The inflammation known to exist in secretory otitis media probably plays an important role (6, 7, 27). Some patients develop tympanosclerosis after mild inflammatory otitis media processes whereas some heal without tympanosclerosis after more aggressive infections. This difference may be due to individual variations in the inflammatory response. The incidence of tympanosclerosis in otitis media varies from 20% to 43% in different clinical series (28, 29). Animal models were developed for development of tympanosclerosis after otitis media. Giles et al. (30) examined the development and progression of tympanosclerosis in rats using a new model for persistent otitis media. Tympanosclerosis developed as a main response to the prolonged otitis media and severity of disease was directly proportional to the duration of otitis media. Flodin et al. (7) inoculated *Streptococcus pneumonia* to the middle ear of the rats. They found that immunocompetent cells and some mediators are presented time-dependently in otitis media and lead to tympanosclerosis development.

Under the electron microscope, tympanosclerosis plaque is seen as an irregular three-dimensional collagen lattice, enclosing spherical mineralized aggregates that are masses of calcium phosphate (6, 31). Although, the calcification process in the middle ear resembles that occurring in atherosclerosis, body may display similar histopathological reactions to different injuries. Healing responses to inflammation were the same, but predisposing factors are different for middle ear and coronary arteries.

Study limitations

This study has the major limitation of including only patients undergoing coronary angiography for suspected CAD. The conclusions do not necessarily apply to patients who have not undergone coronary angiography.

We diagnosed tympanosclerosis in only 14 of 203 patients (6.9%). The number of cases is too limited for broad generalizations. A larger study with more patients is thus necessary to confirm our results.

Conclusion

Inflammation has evolved as a protective response to insult or injury. Both tympanosclerosis and atherosclerosis are the final steps of an inflammatory process, which continues for many years due to a traumatic lesion like endothelial damage or an infection. Although histopathological appearance may be similar in both diseases, these are two different disease affecting different sides of the body with different risk factors. More studies are needed to understand etiological mechanisms and association between these two pathologies.

Conflict of interest: None declared

References

1. Falk E. Pathogenesis of atherosclerosis. J Am Coll Cardiol 2006; 47 (8 Suppl): C7-12.
2. Langheinrich AC, Bohle RM. Atherosclerosis: humoral and cellular factors of inflammation. Virchows Arch 2005; 446: 101-11.
3. Gibb AG. Tympanosclerosis. Proc R Soc Med 1976; 69: 155-62.
4. Wielinga E, Kerr AG. Tympanosclerosis. Rev Clin Otolaryngol 1993; 18: 341-9.
5. Mattson C, Marklund SL, Hellström S. Application of oxygen free radical scavengers to diminish the occurrence of myringosclerosis. Ann Otol Rhinol Laryngol 1997; 106: 513-8.

6. Forseni M, Sjöback DB, Hultcrantz M. A study of inflammatory mediators in the human tympanosclerotic middle ear. Arch Otolaryngol Head Neck Surg 2001; 127: 559-64.
7. Flodin MF, Hultcrantz M. Possible inflammatory mediators in tympanosclerosis development. Int J Pediatr Otorhinolaryngol 2002; 63: 149-54.
8. Koç A, Üneri C. Genetic predisposition for tympanosclerotic degeneration. Eur Arch Otorhinolaryngol 2002; 259: 180-3.
9. Ferri M, Faggioli GL, Ferri GG, Pirodda A. Is carotid stenosis correlated with tympanosclerosis. Int Angiol 2004; 23:144-6.
10. Pirodda A, Ferri GG, Bruzzi C, Marini M, Faggioli G. Possible relationship between tympanosclerosis and atherosclerosis. Acta Otolaryngol 2004; 124: 574-6.
11. Bluestone CD. Definitions, terminology and classification. In: Rosenfeld RM, Bluestone CD, editors. Evidence-Based Otitis Media. 2nd ed. Hamilton & London: BC Decker; 2003. p.120-35.
12. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma without use of the preparative ultracentrifuge. Clin Chem 1972; 18: 499-502.
13. Judkins MP. Selective coronary arteriography: I. A percutaneous transfemoral technique. Radiology 1967; 89: 815-24.
14. Sullivan DR, Marwick TH, Freedmann SB. A new method of scoring coronary angiograms to reflect extent of coronary atherosclerosis and improve correlation with major risk factors. Am Heart J 1990; 119: 1262-7.
15. Komorovsky R, Desideri A. Carotid ultrasound assessment of patients with coronary artery disease: a useful index for risk stratification. Vasc Health Risk Manag 2005; 1: 131-6.
16. Enbergs A, Dorszewski A, Luft M, Mönnig G, Kleemann A, Schulte H, et al. Failure to confirm ferritin and caeruloplasmin as risk factors for the extent of coronary arteriosclerosis. Coron Artery Dis 1998; 9: 119-24.
17. Lowe GO. Different locations of atherosclerosis, different risk factors, different therapies? Pathophysiol Haemost Thromb 2003-2004; 33: 262-6.
18. Fruchart JC, Nierman MC, Stroes ES, Kastelein JJ, Duriez P. New risk factors for atherosclerosis and patient risk assessment. Circulation 2004; 109: III15-9.
19. Pereira IA, Borba EF. The role of inflammation, humoral and cell mediated autoimmunity in the pathogenesis of atherosclerosis. Swiss Med Wkly 2008; 138: 534-9.
20. Wick G, Knoflach M, Xu Q. Autoimmune and inflammatory mechanisms in atherosclerosis. Ann Rev Immunol 2004; 22: 361-403.
21. Mattson C, Marklund SL, Hellström S. Application of oxygen free radical scavengers to diminish the occurrence of myringosclerosis. Ann Otol Rhinol Laryngol 1997; 106: 513-8.
22. Görür K, Özcan C, Polat A, Ünal M, Tamer L, Cinel İ. The anti-oxidant and anti-apoptotic activities of selenium in the prevention of myringosclerosis in rats. J Laryngol Otol 2002; 116: 426-9.
23. Özcan C, Görür K, Cinel L, Talas DÜ, Ünal M, Cinel İ. The inhibitory effect of topical N-acetylcysteine application on myringosclerosis in perforated rat tympanic membrane. Int J Pediatr Otorhinolaryngol 2002; 63: 179-84.
24. Akbaş Y, Pata YS, Görür K, Polat G, Polat A, Özcan C, et al. The effect of L-carnitine on the prevention of experimentally induced myringosclerosis in rats. Hearing Research 2003; 184: 107-12.
25. Koç A, Üneri C. Sex distribution in children with tympanosclerosis after insertion of a tympanostomy tube. Eur Arch Otorhinolaryngol 2001; 258: 16-9.
26. McRae D, Gatland DJ, Youngs R, Cook J. Aspiration of middle ear effusions prior to grommet insertion an etiological factor in tympanosclerosis. J Otolaryngol 1989; 18: 229-31.
27. Forseni M, Eriksson A, Bagger-Sjöback D, Nilsson J, Hultcrantz M. Development of tympanosclerosis: can predicting factors be identified? Am J Otol 1997; 18: 298-303.
28. Tos M, Stangerup SE. Hearing loss in tympanosclerosis caused by grommets. Arch Otolaryngol Head Neck Surg 1989; 115: 931-5.
29. Costa SS, Paparella MM, Schachern PA, Yoon TH, Kimberley BP. Temporal bone histopathology in chronically infected ears with intact and perforated tympanic membranes. Laryngoscope 1992; 102: 1229-36.
30. Giles JJ, Russell JD. Microscopic analysis of experimentally induced tympanosclerosis in the rat. J Anat 2002; 200: 199.
31. Olsson M, Dalsgaard CJ, Haegerstrand A, Rosenqvist M, Ryden L, Nilsson J. Accumulation of T lymphocytes and expression of interleukin-2 receptors in nonrheumatic stenotic aortic valves. J Am Coll Cardiol 1994; 23: 1162-70.