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ORIGINAL ARTICLE

Usability of Achilles tendon strain elastography for the diagnosis of coronary artery disease

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Abstract

Purpose There are close relationships between major coronary artery disease (CAD) risk factors and Achilles tendon thickness (AT-T) and AT strain ratio (AT-SR). Our aim was to evaluate the diagnostic importance of AT-T and AT-SR as obtained by ultrasonography (USG) and strain elastography (SE) for predicting CAD.

Materials and methods One hundred and eighty-four patients scheduled to undergo coronary angiography were included in the study. Achilles tendon USG (B-mode and SE) and laboratory tests were performed on all patients. The patients were divided into two groups, i.e., patients with and without CAD.

Results The patients with CAD (72.8%) were more likely to be male, exhibited higher frequencies of diabetes mellitus (DM) and hyperlipidemia, exhibited higher levels of basal creatinine and glucose, and had higher AT-T and AT-SR values ($p < 0.05$ for all). Age, DM, AT-T, and AT-SR independently predicted the probability of CAD in a logistic regression analysis ($p < 0.05$ for all). Age (each year), DM (presence), AT-T (each 1 mm), and AT-SR (each 0.1) increased the CAD risk by 3.4%, 2.9 times, 47.1%, and 16.0%, respectively. ROC analysis revealed AUCs of 0.665 and 0.730 for the AT-T and AT-SR values, respectively ($p < 0.05$). The AT-SR cutoff value of 1.2 predicted the presence of CAD with 75.4% sensitivity and 72.7% specificity.

Conclusions AT-SR is a simple, inexpensive, noninvasive, reproducible, and objective parameter for the prediction of CAD. We think that AT-SR evaluation should become a part of conventional USG assessments in patients who are at a high risk of CAD.

Keywords Achilles tendon thickness · Achilles tendon strain ratio · Strain elastography · Coronary artery disease

Introduction

Coronary artery disease (CAD) remains the main cause of death worldwide. The male gender, age, obesity, smoking, hypertension (HT), diabetes mellitus (DM), and hyperlipidemia (HL) are the major risk factors for CAD [1]. The prediction of CAD is an important issue. Therefore, many invasive and noninvasive evaluations are being performed.

The Achilles tendon (AT) is the thickest, strongest, and largest tendon in the body. It has very important functions in the activities of the leg [2]. The AT is usually evaluated for trauma by magnetic resonance imaging and ultrasonography (USG) in clinical practice. With the exception of trauma, AT USG is recommended as a follow-up method for familial hyperlipidemia (FH) patients [3–5]. Strain elastography (SE) is a novel USG modality that provides important information

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about tissue stiffness and elasticity [6]. Recently, this new SE method has been used for evaluation of the AT [7–10].

Many studies on the relationships between major CAD risk factors (except HT) and AT thickness (AT-T) and AT strain ratio (AT-SR) have been conducted. According to these studies, AT-T increases with male gender [3, 4, 11], advanced age [7], obesity [8], smoking [9], DM, and HL (especially FH) [3, 4, 11–13].

Most of these studies found a relationship between increased AT-SR and CAD risk factors [7–10]. Additionally, there is a close relation between carotid intima–media thickness (C-IMT) and increased AT-T [4, 11, 13]. All of these relationships made us think that AT USG evaluation results might be useful in predicting CAD. There is no information about the relationships between increased AT-T and AT-SR values and CAD in the literature.

We aimed to investigate the diagnostic importance of AT-T and AT-SR for the prediction of CAD.

Materials and methods

The study protocol was prepared according to the principles of the Declaration of Helsinki. The Local Ethics Committee approved the study protocol, and each participant provided written informed consent.

Study population

A total of 184 patients (116 men, 68 women, mean age 59.1 ± 13.1 years) scheduled to undergo coronary angiography between October 2017 and April 2018 were included in the study. AT USG (B-mode and SE) and routine laboratory tests were performed on all patients. Patients with histories of AT trauma, musculoskeletal disease, immobility problems, rheumatoid arthritis, peripheral vascular and cerebrovascular disease, known CAD, heart valve disease, hemodynamic instability, acute or chronic respiratory problems, heart failure, active thyroid disease, chronic kidney or liver disease, malignancy, active infections, hemorrhagic diathesis, pregnancy, or suspected pregnancy were excluded.

After a detailed assessment of the medical histories and complete physical examinations, the baseline characteristics of patients, including age, sex, HT, DM, HL, current smoking status, body weight and height, and body mass index (BMI), were recorded for all patients. The complete blood counts, glucose and lipid levels, and renal and liver functions were recorded from routinely collected blood samples.

At study entry, fasting total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides were measured using standard automated laboratory methods (Abbott Aeroset, MN, USA) and using appropriate commercial kits (Abbott). Presence of HT was diagnosed according to ESC 2013 guideline [14]. The 2016 ADA guidelines were used for DM diagnosis [15]. Patients who had glycated hemoglobin (HbA1c) levels ≥ 6.5%, fasting plasma glucose ≥ 126 mg/dL, and 2nd h plasma glucose with 75 g OGTT ≥ 200 mg/day were assessed as having type II DM.

FH score is a widely used scoring system to diagnose heterozygous FH. In the FH scoring system, the patient's family history, clinical history, physical examination findings, and LDL-C levels are used. From a maximum of 24 points, patients with higher than 8 points are assessed as "definite FH," patients with 6–8 points are assessed as "probable FH," patients with 3–5 points are assessed as "possible FH," and patients with < 3 points are assessed as "no FH" [16]. Angiography was performed using a Siemens Coronary Angiography System (Axiom Sensis XP, Berlin, Germany) and standard techniques in our clinic. Coronary artery disease was defined as ≥ 50% stenosis of at least one major epicardial artery. The patients were divided into two groups, i.e., those with CAD and without CAD.

Achilles tendon ultrasonography

AT USG examinations were performed by two experienced radiologists using a high-resolution ultrasound Doppler system (Philips EPIQ 7) equipped with a high-resolution linear converter (12-5 MHz) (Philips Health Care, Bothell, WA, USA). The AT B-mode USG evaluation was performed while the patient was lying in the prone position with both feet passed through the edge of the examination table freely, with the ankle at approximately 90° plantar flexion and the ATs at rest.

AT-T was calculated according to the maximum distance between the anterior and posterior walls, and AT width was measured as the distance from the medial to the lateral wall in the transverse plane at the level of the medial malleolus (Fig. 1) [17]. The ultrasound scanner setting for penetration depth was set to 2.5 cm and 4 cm to be useful for every patient for all B-mode and elastography USG examinations, respectively.

AT SE evaluations were performed in the same position. Short repetitive manual compressions were applied to the AT with care to avoid anisotropy. The compression amount and uniformity were standardized using pressure graphics. After at least three compression–relaxation cycles, SE calculations were performed based on the best images. Color scales and predefined AT-SR elastographic findings were used [18, 19]. AT stiffness was graded automatically by our USG device. These grades were as follows: Grade 1: red to yellow (hardest or hard tissue), Grade 2: green (intermediate tissue), and Grade 3: blue (soft tissue; Fig. 2a–c). Local AT-SR calculations were performed on the same images. This calculation was compared with a reference adipose tissue that was taken

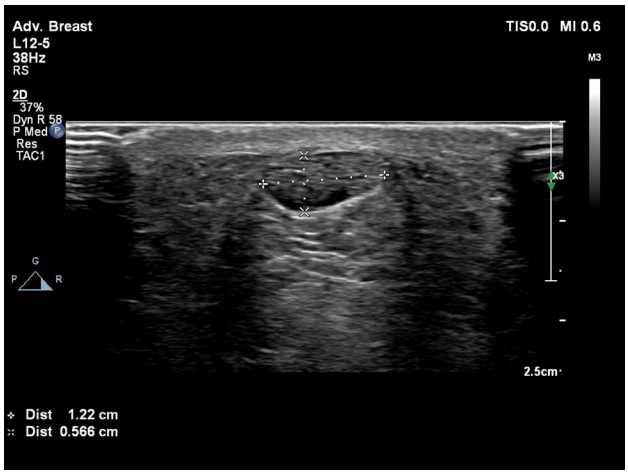

Fig. 1 Achilles tendon thickness measurement with B-mode ultrasonography. The Achilles tendon thickness was measured via evaluation of the anteroposterior diameter in a transverse view at the level of the medial malleolus

from the Kager's fat pad located at the posterior tendon [20]. The first region of interest (ROI) (A) was placed in the reference adipose tissue, and the other ROIs were placed on the AT (B). To make the second ROI or Strain 2 (B) standard in all patients, care was taken to measure AT-T in the midline of the AT at the medial malleolar level.

The strain ratio (B/A) was automatically calculated (Fig. 3a, b). AT-SR was compared with an adjacent reference tissue and semiquantitatively evaluated. Three consecutive measurements were made for each AT, and mean values were calculated from the results from both legs. The subjects were blindly evaluated by two experienced radiology specialists.

Statistical analysis

All analyses were performed using SPSS 22.0 (SPSS for Windows 17.0, Chicago, IL, USA). The data are expressed as the means ± the SDs for continuous variables

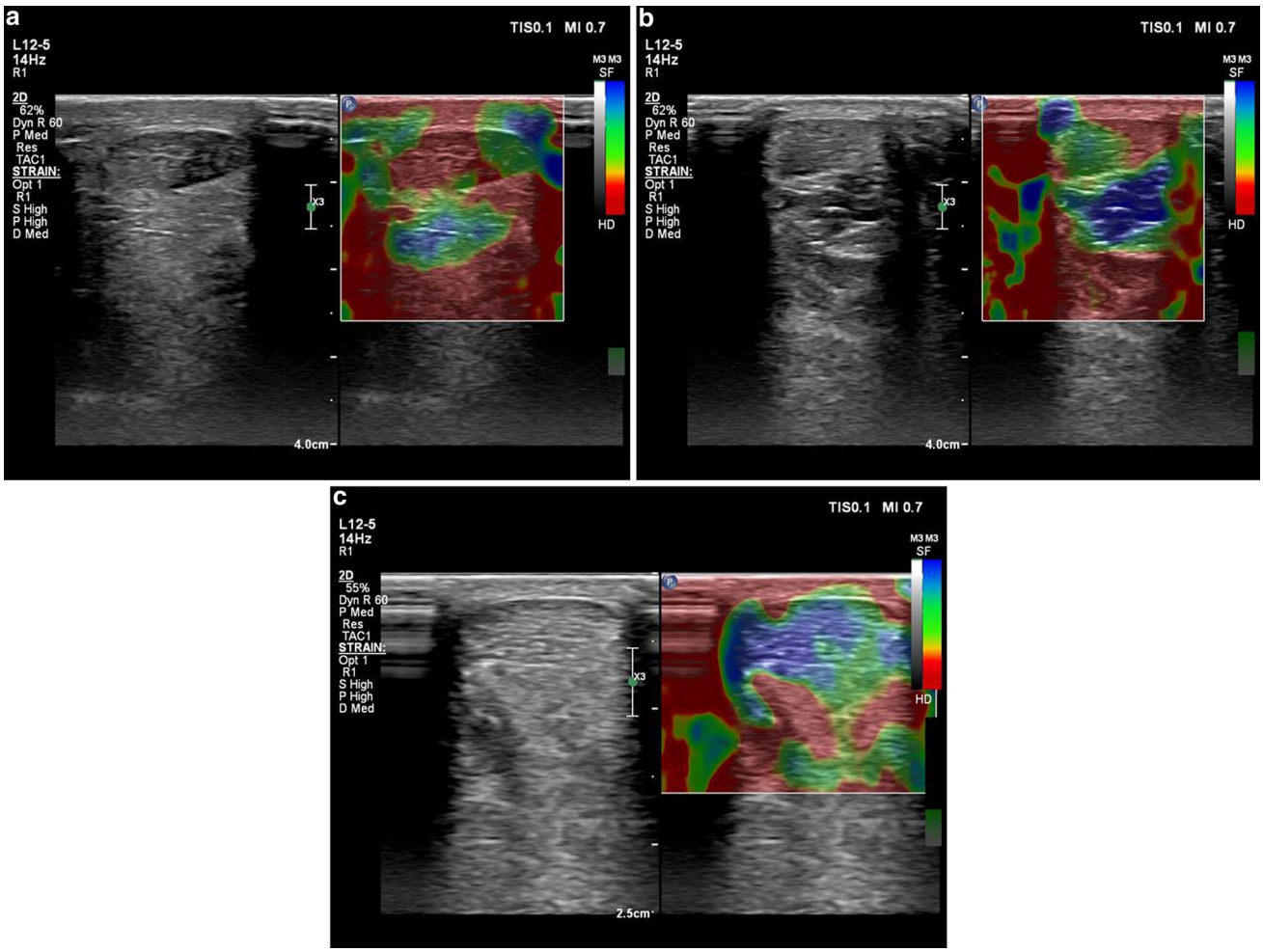

Fig. 2 Different elastography color grades of the Achilles tendon. **a** Grade 1: red to yellow (hardest or hard tissue). **b** Grade 2: green (intermediate tissue). **c** Grade 3: blue (soft tissue)

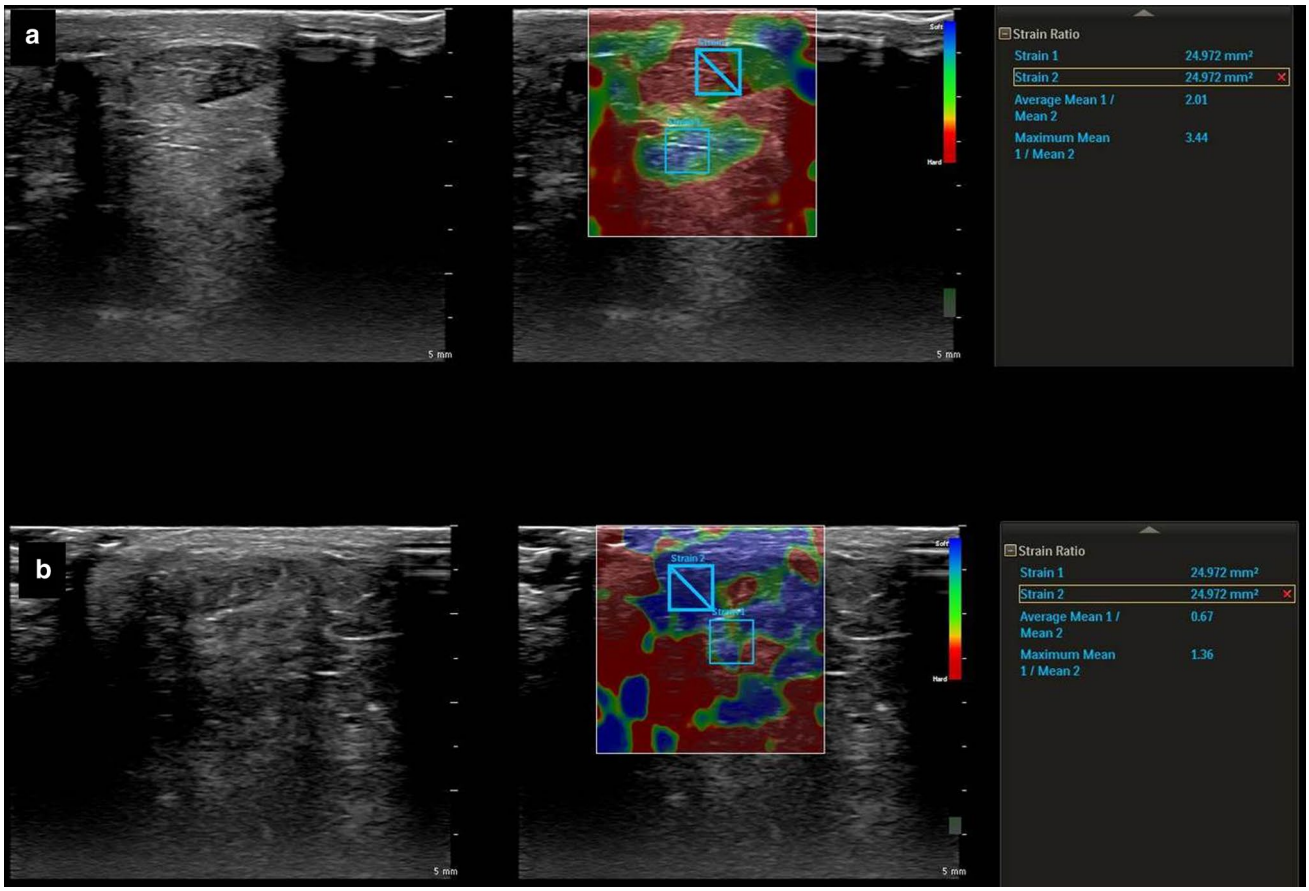

Fig. 3 Achilles tendon strain ratio measurement by strain elastography. The strain ratio measurements at the level of the medial malleolus (region of interest) and the reference region (Kager's fat pad, posterior wall of the AT) from **a** a CAD patient and **b** a non-CAD patient. The software of the ultrasound machine was used to calculate the strain ratio

and as percentages for categorical variables. The Kolmogorov–Smirnov test was used to determine whether the continuous variables were normally distributed. The normally distributed continuous variables were compared using Student's *t* test. The categorical variables were compared with the Chi square test. For multiple comparisons of groups' proportions, Bonferroni-corrected *z* test was used. Pearson's and Spearman's correlations were used to examine the relationships of the AT-Ts and AT-RSs with the continuous variables. Multivariate logistic regression analysis was used to determine the independent predictors of CAD. All significant parameters in the univariate analysis were included in the multivariate model. A receiver operator characteristic (ROC) curve analysis was performed to identify the optimal cutoff points for AT-T and AT-SR. The areas under curves were calculated to test the accuracies of the analyses. A p value < 0.05 was considered statistically significant.

Results

Coronary artery disease was present in 134 patients (72.8%). Cohen kappa values that evaluate interobserver variability were over 90% for all US parameters. Coefficient of variation for AT-T and AT-SR was 19.3% and 39.3%, respectively.

Demographic and laboratory comparisons of patients with and without CAD

The patients with CAD were significantly older, were more likely to be male, and exhibited higher frequencies of DM and HL ($p < 0.05$, Table 1). The serum creatinine and glucose levels were significantly higher in patients with CAD ($p < 0.05$, Table 1). Among all the subjects included in the

Table 1 Clinical and laboratory characteristics of the study populations with and without CAD

	Patients with CAD $n=138$	Patients without CAD $n=46$	p
Age (years)	60.3 ± 12.9	55.2 ± 13.3	0.021
Gender (male)	94	22	0.013
Office systolic BP (mmHg)	126.4 ± 20.1	128.9 ± 12.1	0.318
Office diastolic BP (mmHg)	76.2 ± 11.6	78.7 ± 7.8	0.100
Heart rate (beat/min)	82.3 ± 13.1	79.7 ± 8.6	0.123
Weight (kg)	80.5 ± 13.8	82.4 ± 12.1	0.014
Height (cm)	169.7 ± 8.2	168.1 ± 11.3	0.391
BMI (kg/m^2)	27.9 ± 4.2	29.3 ± 4.9	0.061
Smoking *n*, (%)	55 (39.9%)	15 (32.6%)	0.243
Hypertension *n*, (%)	77 (55.8%)	21 (45.7%)	0.153
Diabetes mellitus *n*, (%)	67 (48.6%)	8 (17.4%)	< 0.001
Hypercholesterolemia *n*, (%)	56 (40.6%)	8 (17.4%)	0.003
Glucose (mg/dL)	131.2 ± 40.9	112.5 ± 18.8	0.003
BUN (mg/dL)	34.7 ± 6.7	33.5 ± 7.6	0.428
Creatinine (mg/dL)	0.89 ± 0.29	0.80 ± 0.18	0.034
Alanine aminotransferase (μ/L)	21.8 ± 12.8	19.2 ± 10.3	0.164
Aspartate aminotransferase (μ/L)	23.3 ± 26.3	21.6 ± 7.13	0.178
Total cholesterol (mg/dL)	190.8 ± 54.2	198.8 ± 36.5	0.260
LDL cholesterol (mg/dL)	132.0 ± 40.7	138.5 ± 28.7	0.236
HDL cholesterol (mg/dL)	41.9 ± 10.8	44.8 ± 10.9	0.113
Triglyceride (mg/dL)	197.8 ± 97.7	208.9 ± 87.2	0.100
White blood cell count (1000/mm^3)	9.2 ± 2.8	9.9 ± 2.01	0.481
Hemoglobin (g/dL)	13.3 ± 2.39	13.3 ± 1.72	0.956
WHO FH score	2.24 ± 2.16	0.98 ± 1.63	< 0.001

BMI body mass index, *BUN* blood urea nitrogen, *CAD* coronary artery disease, *FH* familial hyperlipidemia, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *WHO* World Health Organization

study, three patients with CAD met the criteria for "definite FH" in the WHO FH scoring. Patients with CAD had significantly higher WHO FH scores than those without CAD ($p < 0.05$, Table 1).

Achilles tendon ultrasonography findings from patients with and without CAD

Patients with CAD had significantly higher AT-T and AT-SR values ($p < 0.05$, Table 2). Additionally, Achilles elastographic color grade I was significantly more common and Achilles elastographic grade III was significantly less common in patients with CAD according to the Achilles SE color scale ($p < 0.05$, Table 2). Achilles elastographic color grade II was similar between the two groups ($p > 0.05$, Table 2).

Table 2 B-mode ultrasonography and strain elastography imaging of the Achilles tendons in patients with and without CAD

	Patients with CAD $n=138$	Patients without CAD $n=46$	p
Achilles tendon thickness (mm)	5.26 ± 0.92	4.71 ± 1.10	0.003
Achilles tendon width (mm)	14.8 ± 2.2	14.5 ± 2.1	0.435
Achilles elastographic color grade I (*n*, %)	48 (35%)	6 (13%)	< 0.05
Achilles elastographic color grade II (*n*, %)	60 (43%)	17 (37%)	> 0.05
Achilles elastographic color grade III (*n*, %)	30 (22%)	23 (50%)	< 0.05
Achilles tendon strain ratio	1.56 ± 0.57	1.16 ± 0.47	< 0.001

CAD coronary artery disease

Table 3 Independent risk factors for the presence of CAD according to multivariate regression analysis

	Odds ratio	95% confidence interval	*p*
Diabetes mellitus (presence)	2.900	1.212–7.125	0.018
Age (year)	1.034	1.001–1.069	0.046
Achilles tendon strain ratio (each 0.1 increase)	1.160	1.064–1.266	0.001
Achilles tendon thickness (mm)	1.471	1.983–2.201	0.049

CAD coronary artery disease

Table 4 ROC curve analysis for the prediction of CAD

Variable	AUROC curve	*p*	Cut-off	Sensitivity (%)	Specificity (%)
Achilles tendon thickness	0.665 (0.562–0.767)	0.001	5 mm	63.0	65.2
Achilles tendon strain ratio	0.730 (0.640–0.820)	< 0.001	1.20	75.4	72.7

CAD coronary artery disease

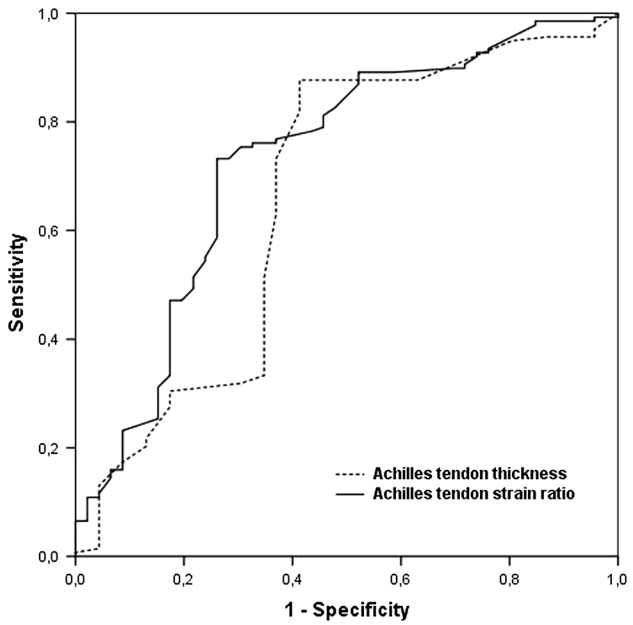

Fig. 4 ROC curve for Achilles tendon strain ratio (solid line) and Achilles tendon thickness (dotted line) for determining patients with coronary artery disease

Prediction of coronary artery disease

Age, DM presence, AT-T, and AT-SR independently predicted CAD in the multivariate logistic regression analysis (Table 3). According to this analysis, increased age (each year), DM (presence), increased AT-T (each 1 mm), and increased AT-SR (each 0.1) increased the risk of CAD by 3.4%, 2.9 times, 47.1%, and 16.0%, respectively (Table 3).

ROC analyses of Achilles tendon thickness and strain ratio

The areas under the curves were 0.665 and 0.730 in the ROC analyses of AT-T and AT-SR values, respectively ($p < 0.05$, Table 4). The receiver operating characteristic curves are presented in Fig. 4. The cutoff value for AT-T was 5 mm, which yielded a sensitivity of 63% and a specificity of 65.2%. The AT-SR cutoff value was 1.20, which yielded a sensitivity of 75.4% and a specificity of 72.7% (Table 4).

Relation between classic coronary artery disease risk factors and Achilles tendon ultrasonography findings

There was no significant relation between age and AT-T or AT-SR ($p > 0.05$ for both). Male patients exhibited significantly higher AT-T (5.33 ± 0.88 for males vs 4.78 ± 1.06 for females, $p = 0.001$) and AT-SR values (1.54 ± 0.63 for males vs 1.33 ± 0.41 for females, $p = 0.010$). AT-T was significantly higher in men with CAD than in those without CAD (5.48 ± 0.76 vs 4.65 ± 1.09, $p = 0.002$). However, AT-T was similar between women with and without CAD ($4.79 \pm 0.1.05$ vs 4.77 ± 1.11, $p = 0.924$). AT-SR was also significantly higher in men with CAD than in those without CAD (1.62 ± 0.64 vs 1.16 ± 050, $p = 0.002$). Similarly, AT-SR was significantly higher in women with CAD than in those without CAD (1.43 ± 0.36 vs 1.15 ± 045, $p = 0.008$). There were no differences in AT-T or AT-SR between patients with and without HT. Diabetic patients had significantly higher AT-T values than the nondiabetic patients (5.34 ± 1.02 vs 4.97 ± 0.94, respectively; $p = 0.013$) and higher AT-SR values (1.60 ± 0.56 vs 1.37 ± 0.56, respectively; $p = 0.006$). Similarly, AT-T (5.32 ± 0.92 vs 5.02 ± 1.01, $p = 0.046$) and AT-SR (1.63 ± 0.66 vs 1.37 ± 0.50, $p = 0.008$) were significantly higher in patients

with hyperlipidemia. AT-T values were similar in the smoking and nonsmoking patients. However, AT-SR was significantly elevated in the smoking patients (1.60 ± 0.63 vs 1.37 ± 0.52, $p = 0.012$). There was no significant relation between BMI and AT-T. However, a significant positive correlation was identified between BMI and AT-SR ($r = 0.145$ and $p = 0.049$).

Discussion

The main finding of the present study is that increased AT-SR as assessed by SE independently predicted the presence of CAD. To our knowledge, this is the first study to identify a relationship between AT-SR and CAD. The AT-SR cutoff value of > 1.2 was able to predict the presence of CAD with an acceptable sensitivity and specificity.

Due to its easily accessible location, AT is radiologically evaluated in many diseases. The best evaluation method for AT is USG [21]. Strain elastography is a new USG modality and it provides important information about the stiffness of different tissues and lesions [6]. This method is also used for evaluation of the elastic properties of AT [7–10]. Smoking, HL, DM, obesity, and advanced age were found to be associated with increased AT-SR. There is no information about the relationships of AT-T, AT-SR, and HT. The pathophysiological effects of the CAD risk factors associated with increased AT-T and AT-SR are very similar to those of coronary atherosclerosis [13, 21–23]. Therefore, evaluation of AT-T and AT-SR could represent a noninvasive method for the prediction of CAD.

It has been reported that smoking decreases AT-T and AT-SR [9]. It has been hypothesized that increased nicotine results in decreased prostaglandin synthesis and increased vasoconstriction. Over time, this vasoconstriction causes relative ischemia, progressive fibrosis, and atrophy in AT [9, 24]. In addition, in one study, nicotine was believed to be responsible for increased cross-linked collagen content, causing fibrosis in interstitial myocardial tissue [25]. In the present study, we found similar AT-T values between the smoking and nonsmoking groups. We also observed that AT-SR increased with smoking.

This result suggests that smoking increases AT-SR by increasing the amount of collagen in the AT, similar to the other tissues of the body. According to many studies, FH is associated with increased AT-T [3, 4, 11–13]. The main reason for this association is systemic lipid accumulation in the AT. Xanthomas in this location are used in the diagnosis of FH. Two different studies have reported that AT-T > 5.8 mm is useful for the diagnosis of FH [3, 4]. LDL cholesterol levels are consistently high and are characterized by corneal, xanthomas, and early coronary artery disease (CAD). There are two different clinical forms of FH: heterozygous and homozygous. The homozygous form is seen at a frequency of 1/1,000,000 and the heterozygote form at a frequency of 1/500 [26, 27]. Two recent large-scale studies have reported a FH incidence of 2.7% in patients undergoing coronary angiography due to acute coronary syndrome and angina [28, 29]. In our study, only three patients were found to have FH according to WHO criteria. Therefore, these patients were not evaluated separately. AT-T and AT-SR were significantly higher in our HL patients. To the extent of our knowledge, there is no information about the association of increased AT-SR in patients with HL in the literature. Additionally, we reported that AT-T > 5 mm could predict CAD with an acceptable sensitivity and specificity. Men have greater AT-Ts than women according to studies [3, 4, 11]. It has been proposed that the higher BMIs of men could be the main reason for this difference. Similarly, we observed that the men had higher AT-Ts in our study. However, because AT-T is thicker in men and the frequency of CAD is higher, the value of AT-T is less important in determining CAD.

Additionally, AT-SRs were also higher in men. All body parts and functions begin to deteriorate with aging. The AT elastic properties diminish with age [30]. The extracellular matrix components increase with aging in a manner similar to the changes in arterial walls [31]. AT-SR has also been found to increase with aging in a recently conducted study [7]. We did not find a significant relation between age and AT-T or AT-SR in our study. We believe that the lower mean age of our study group compared with those of other studies could be the main reason for this finding. An increase in advanced glycation end products is very important in the development of macrovascular complications, such as CAD, in DM patients [32]. In diabetic patients, a similar mechanism plays a role in increased AT-T and AT-SR [10]. Similarly, we found significantly increased AT-T and AT-SR values in our DM patients. AT-T is increased in obese patients. Due to structural changes, AT-SR is also increased dramatically in obese patients [8]. We did not specifically evaluate obese patients in our study. However, we observed a significant positive relation between AT-SR and BMI.

Carotid IMT is a useful and valid parameter for the diagnosis of atherosclerosis [33]. Dimitrios et al. [13] reported that there was a positive correlation between increased C-IMT and AT-T. These authors also stated that both clinical situations occurred due to the same clinical and biochemical pathophysiology. This finding was supported by another later study [11]. Xanthomas are usually located around the AT [21]. Michikura et al. [4] reported that there was a positive correlation between IMT and AT-T in their FH group, but not in their non-FH group. Therefore, we hypothesized that we could use the same area for the diagnosis of CAD. The lipid cores of xanthomas and advanced coronary atherosclerotic lesions are similar according to histochemical studies [21]. Additionally, it was reported that lipid depositions

at both sites originated from serum lipids [22]. Moreover, it has been determined that macrophages that accumulate oxidized LDL cholesterols are primarily responsible for the pathophysiologic processes that occur in the AT and atherosclerotic coronary arteries [21, 23].

Briefly, we determined that the major CAD risk factors, with the exceptions of HT and age, were closely related to increased AT-T and AT-SR. As a result of these findings, we hypothesized and verified that AT-SR was an independent predictor of CAD.

Limitations

Our study had some important limitations. Strain ratio evaluation is an operator-dependent approach. Our study was conducted by two experienced specialists. We did not evaluate patients with peripheral vascular or cerebrovascular diseases. Exercise is an important determinant of the properties of AT [34]. Previous physical activities were not recorded in our study. We did not perform histopathologic evaluations of our subjects. In a previous study, it was determined that histologic and SE findings were closely related [35]. Some studies have measured AT-SR from three different sites of AT, and all of these studies reported similar results from all sections [7, 9, 10]. We performed our measurements only at the level of the medial malleolus and in the transverse view, because we did not want to create confusion with measurements and cutoff values from three different sections.

Conclusion

AT-SR was significantly increased in patients with CAD. An independent association was found between AT-SR and the presence of CAD, and AT-SR can easily be detected by SE. AT-SR is thus considered to be a simple, inexpensive, noninvasive, reproducible, and objective parameter for the prediction of CAD. We think that AT-SR evaluations should become a part of conventional USG assessments in patients who are at a high risk of CAD. Moreover, patients with AT-SRs > 1.2 should be closely followed for possible CAD.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests or sources of funding.

Ethical statement All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Informed consent Informed consent was obtained from patients for being included in the study.

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