The Use of Achilles Tendon Sonography to Distinguish Familial Hypercholesterolemia from Other Genetic Dyslipidemias

Mireia Junyent, Rosa Gilabert, Daniel Zambón, Isabel Núñez, Maríà Vela, Fernando Civeira, Miguel Pocoví, Emilio Ros

Objective—Achilles tendon (AT) xanthomas, specific for familial hypercholesterolemia (FH), may be clinically undetectable. We assessed the usefulness of AT sonography in the diagnosis of FH.

Methods and Results—Sonographic AT characteristics were evaluated in 127 subjects with FH (81 genetically ascertained), 84 familial combined hyperlipidemia, 79 polygenic hypercholesterolemia, and 88 normolipidemic controls. Abnormal echostructure (sonographic xanthoma) was noted only in FH. AT thickness was higher (P<0.001) in FH men and women compared with all of the other groups and, in FH mutation carriers but not in others, correlated positively with low-density lipoprotein cholesterol (r=0.345; P<0.001) and negatively with high-density lipoprotein cholesterol (r=−0.265, P=0.015). Thickness thresholds for the diagnosis of FH with specificity >80%, as were derived from receiver operating curves, were 5.3 and 5.7 mm in men < and >45 years, and 4.8 and 4.9 mm in women < and >50 years, respectively. In FH mutation carriers, sonographic findings increased the clinical diagnosis of xanthomas from 35 (43%) to 55 (68%). Using thresholds in validation sets of 70 genetically identified FH and 54 dyslipidemic non-FH correctly classified 80% and 88%, respectively.

Conclusion—Sonographic AT characteristics are normal in non-FH dyslipidemias. Identification of suspected FH by ultrasound using sex- and age-specific AT thickness thresholds is recommended. (Arterioscler Thromb Vasc Biol. 2005;25:2203-2208.)

Key Words: Achilles tendon ■ xanthomas ■ familial hypercholesterolemia ■ genetic dyslipidemias ■ ultrasonography

Heterozygous familial hypercholesterolemia (FH) is an autosomal-dominant inherited disorder of lipid metabolism characterized by lifelong elevation of serum cholesterol that is usually caused by defects in the low-density lipoprotein (LDL) receptor (LDLR) gene.1 Clinical features include early coronary heart disease (CHD) and tendon xanthomas because of accelerated cholesterol deposition within both vascular and extravascular tissues. Tendon xanthomas are specific for FH, and the Achilles tendon (AT) is the usual location.1–3

Xanthomas are composed of monocyte-derived foam cells resulting from intracellular accumulation of lipids and connective tissue.4 In genetically ascertained heterozygous FH, xanthomas diagnosed by physical examination begin to appear after the second decade of life2 and are found in 20% to 50% of affected adults in unselected cohorts.5–7 It is unknown why some FH subjects disclose xanthomas and others do not, even while having similar LDL cholesterol levels and sharing the same LDLR defect.5 One reason may be that physical examination has shortcomings because their clinical identification as diffuse enlargements or nodular deformities in the AT or other locations is not always easy.

When available, genetic testing may secure the etiologic diagnosis of FH.2,3 Otherwise, objective sets of clinical criteria, as defined by the United Kingdom Simon Broome Register Group,8 the United States Make Early Diagnosis to Prevent Early Death Program,9 or the Dutch Lipid Clinic Network,10 are used. These diagnostic criteria are based on pretreatment lipid values, family history, and clinical manifestations. The presence of tendon xanthomas weighs heavily in the United Kingdom and Dutch scoring systems, signifying a definite diagnosis.8,10 A reason why their identification is crucial for diagnosing FH in clinical practice. Ultrasonography, a simple, affordable, and rapid imaging technique, has been used to reproducibly assess AT thickness and improve on the clinical diagnosis of xanthomas.11–16 However, the
TABLE 1. Characteristics of Study Groups

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Normolipidemic Controls (n=88)</th>
<th>Moleculary Defined FH (n=81)</th>
<th>FH with No Genetic Defect (n=46)</th>
<th>Familial Combined Hyperlipidemia (n=84)</th>
<th>Polygenic Hypercholesterolemia (n=79)</th>
<th>FH Validation Set from Zaragoza (n=70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (range)</td>
<td>48 (26–81)</td>
<td>45 (26–76)</td>
<td>51 (27–79)</td>
<td>48 (30–67)</td>
<td>51 (29–71)</td>
<td>47 (26–82)</td>
</tr>
<tr>
<td>Men/women, n/n</td>
<td>37/51</td>
<td>45/36</td>
<td>24/22</td>
<td>55/29</td>
<td>39/40</td>
<td>31/39</td>
</tr>
<tr>
<td>Family history of CHD, n (%)</td>
<td>11 (13)</td>
<td>41 (50)</td>
<td>21 (45)</td>
<td>53 (63)</td>
<td>23 (29)</td>
<td>39 (58)</td>
</tr>
<tr>
<td>Personal history of CHD, n (%)</td>
<td>0</td>
<td>19 (23)</td>
<td>10 (22)</td>
<td>16 (19)</td>
<td>12 (15)</td>
<td>9 (13)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>68.6±11.3</td>
<td>69.6±10.9</td>
<td>68.6±10.2</td>
<td>74.4±11.4</td>
<td>71.1±11.2</td>
<td>68.4±10.6</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>25.8±4.2</td>
<td>25.7±3.5</td>
<td>25.7±3.1</td>
<td>26.3±3.1</td>
<td>26.4±3.3</td>
<td>25.1±4.1</td>
</tr>
<tr>
<td>Ever smoked, n (%)</td>
<td>23 (26)</td>
<td>36 (44)</td>
<td>23 (50)</td>
<td>57 (68)</td>
<td>39 (49)</td>
<td>49 (70)</td>
</tr>
<tr>
<td>Arterial hypertension, n (%)</td>
<td>8 (9)</td>
<td>7 (9)</td>
<td>7 (15)</td>
<td>27 (32)</td>
<td>21 (27)</td>
<td>8 (11)</td>
</tr>
<tr>
<td>Diabetes mellus, n (%)</td>
<td>0</td>
<td>0</td>
<td>1 (2)</td>
<td>8 (10)</td>
<td>7 (9)</td>
<td>0</td>
</tr>
<tr>
<td>Tendon xanthomas, n (%)</td>
<td>—</td>
<td>35 (43)*</td>
<td>10 (22)</td>
<td>—</td>
<td>—</td>
<td>33 (35)</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>196±25</td>
<td>392±83</td>
<td>345±57</td>
<td>307±54</td>
<td>286±34</td>
<td>397±64</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>129±21</td>
<td>310±80</td>
<td>259±60</td>
<td>210±48</td>
<td>205±32</td>
<td>320±34</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>55±15</td>
<td>55±19</td>
<td>55±14</td>
<td>43±12</td>
<td>53±14</td>
<td>54±15</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>90 (68–120)</td>
<td>115 (84–166)</td>
<td>119 (92–167)</td>
<td>259 (198–338)</td>
<td>128 (95–176)</td>
<td>93 (68–121)</td>
</tr>
<tr>
<td>Apo B, g/L</td>
<td>1.04±0.25</td>
<td>2.11±0.54</td>
<td>2.00±0.39</td>
<td>1.80±0.35</td>
<td>1.61±0.27</td>
<td>—</td>
</tr>
<tr>
<td>Apo E genotypes, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E2/E3</td>
<td>7 (8.6)</td>
<td>3 (6.5)</td>
<td>13 (15.5)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>E3/E3</td>
<td>59 (72.8)</td>
<td>33 (71.7)</td>
<td>57 (67.9)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>E4/E3, E4/E4</td>
<td>14 (17.3)</td>
<td>8 (17.4)</td>
<td>13 (15.5)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>E2/E4</td>
<td>1 (1.2)</td>
<td>2 (4.3)</td>
<td>1 (1.2)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Values are mean±SD except for triglycerides (median and interquartile ranges).

*All subjects had Achilles tendon xanthomas; 7 had associated xanthomas in other locations (4 knuckles, 2 elbows, and 1 pretilibial).

ultrasound characteristics of AT in other genetic dyslipidemias disclosing elevated blood cholesterol levels that might easily lead to a suspicion of FH have not been evaluated. The aim of this study was to assess the usefulness of AT sonography to distinguish genetically ascertainment FH from clinical FH without a molecular diagnosis and other genetic dyslipidemias in comparison with normolipidemic subjects.

Methods

Subjects

From March 2000 to April 2005 we evaluated 290 consecutive adults with a diagnosis of primary hypercholesterolemia attending the Lipid Clinic of Hospital Clinic, Barcelona. Depending on family history, physical signs, and lipid levels, subjects were given a clinical diagnosis of FH, familial combined hyperlipidemia (FCH), or polygenic hypercholesterolemia (Table 1). Subjects were referred for diagnosis or because of refractoriness to treatment, and they had no effective cholesterol-lowering therapy before recruitment. None gave a history of AT tears or tendonitis.

For identifying FH in 127 subjects, we applied the Dutch criteria.10 Individuals were recruited into the Spanish FH Register 17 and gave a history of AT tears or tendonitis.

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Clinical and Laboratory Characteristics

All of the subjects were assessed for standard cardiovascular risk factors (Table 1). Xanthomas were searched at the usual locations (dorsum of the hands, elbows, pretilib tuberosities, and AT) by the same physicians (D.Z. and E.R.) and were considered to be present if tendons appeared diffusely enlarged or had focal nodularities. When findings were equivocal, ATs were recorded as normal. To obtain a baseline lipid profile, fasting blood was drawn after at least 4 weeks off of hypolipidemic drug treatment. Cholesterol and triglycerides were determined by standard enzymatic methods. LDL cholesterol was estimated with the Friedewald equation except in subjects with triglycerides >300 mg/dL, when it was measured by ultracentrifugation techniques as described.20 In those suspected of being FH or FCH carriers, apo E genotyping was performed using the method of Wenham et al.21 All of the participants gave written informed consent to a protocol approved by the local review board.

Ultrasoundographic Examination

AT sonography was performed in all of the subjects at recruitment by trained sonographers (R.G. and I.N.) using Toshiba equipment (SSA 270A, SSA 140A, Powervision, Aprio) and multifrequency (7–10 MHz) electronic linear array transducers. ATs were examined with the subjects lying prone, with ankles extended beyond the examination bed and feet at 90° flexion. Special attention was paid to holding the probe perpendicular to the tendon. Measurements of thickness
(average of both feet) were made from both sagittal and transverse scans at the point of maximum thickness. Breadth measures were taken from transverse scans. In uniformly sized tendons, measurements were taken 2 cm proximally to insertion in the os calcis. We also classified AT echostructure as one of the following 2 categories: normal, when the fibrillar structure of the tendon was preserved; and xanthoma, when fibrillar structure was lost and/or single, or multiple, echolucent areas were detected within12–15,22 (see http://atvb.ahajournals.org). We evaluated the interobserver variation for thickness and breadth in 15 subjects and found correlation coefficients of 0.91 and 0.86, respectively.

Statistical Analyses
Numerical variables are expressed as mean±SD. Quantitative AT variables were evaluated by sex with ANCOVA analyses, using post-hoc Bonferroni testing for assessment of group differences. Pearson’s correlation coefficients were constructed to test relationships between continuous variables. We determined sex- and age-specific AT thickness threshold values for diagnosing FH based on the analysis of receiver operator characteristics (ROC) curves. ROC curves were constructed by using FH mutation carriers as the disease group and the pooled non-FH subjects as the nontdisease group. A P value <0.05 was conventionally used to indicate statistical significance. SPSS software (version 11.0) was used for statistical analyses.

Validation Sets
A series of 70 FH mutation carriers from Hospital Miguel Servet, Zaragoza (Table 1), who underwent sonographic evaluation of AT thickness with the same protocol, were used to validate the performance of thresholds obtained in Barcelona. The LDLR defects in this group, determined following the same Spanish FH Register protocol,23 were from 36 different types and encompassed 31 missense, 14 nonsense, 13 splicing, and 12 frameshift mutations. A single subject carried the mutation R3500Q in APOB.

An additional group of 54 non-FH subjects (29 men and 25 women) from Hospital Miguel Servet with sonographic evaluation of AT thickness was used to identify the proportion of false positives obtained with the thresholds determined in the Barcelona study. They were 25 subjects with a clinical diagnosis of FH and 29 with polygenic hypercholesterolemia, with an overall age of 48±12 years and mean levels of total, LDL, and HDL cholesterol of 295±34 mg/dL, 223±36 mg/dL, and 46±16 mg/dL, respectively, and triglycerides of 186±134 mg/dL. AT thickness measurements were performed with an ALOKA SSD-900 sonographer using a 7.5-MHz linear-array probe. Tendon echostructure was not evaluated in the Zaragoza subjects.

Results
Clinical Features and Lipid Profiles
Table 1 shows the demographic and clinical characteristics and lipid profiles of the study groups. FH mutation carriers were slightly younger than the other groups, and the sex distribution differed in normolipidemic subjects, where women predominated, and FCH, where there were more men. As expected, FH and FCH subjects frequently had a family history of premature CHD. Also, subjects with FCH and polygenic hypercholesterolemia were heavier than those of other groups. Tendon xanthomas were detected by physical examination only in FH. Lipid values were consistent with the clinical diagnoses, with markedly elevated total cholesterol, LDL cholesterol, and apo B in the FH groups; high cholesterol, triglycerides, and apo B together with low HDL cholesterol in FCH, and lesser cholesterol elevation in polygenic hypercholesterolemia. Apo E genotypes were determined in FH and FCH subjects from Barcelona but were not available in the FH validation group from Zaragoza. Except for an overrepresentation of E2 in FCH, the distribution of apo E genotypes was similar in the 3 groups. There were no E2/E2 genotypes in these series.

Sonographic Findings
Sonographic AT xanthomas were observed only in subjects with FH, being present in 32 mutation carriers (40%) and 11 without an identified LDLR or APOB defect (24%). Table 2 shows the unadjusted values of sonographic tendon thickness and breadth in the groups studied. Men had thicker and larger tendons than women, a difference that remained after the adjustment of values for age, weight, and LDL cholesterol (data not shown). For the 2 sexes, both tendon thickness and breadth were essentially similar in controls, FCH, and polygenic hypercholesterolemia, whereas unadjusted and age- and weight-adjusted AT thickness and breadth were significantly (P<0.05) higher in genetically ascertained FH subjects compared with all of the other groups. FH individuals with no genetic defect identified had measures in between. Additionally, adjusting measurements for LDL cholesterol attenuated this effect. FH men with an identified mutation still had thicker and larger ATs (P<0.05) than subjects with FCH or polygenic hypercholesterolemia (data not shown).

Tendon thickness and breadth were strongly correlated (r=0.79; P<0.001). As shown in the Figure, AT thickness was unrelated to age in all of the study groups. On the other hand, both AT thickness and breadth correlated significantly (P<0.005) to body weight in all of the groups (r=0.301–0.475). Whereas quantitative tendon measures were unrelated (P>0.2) to lipid values in non-FH groups, AT thickness and breadth showed positive correlations with LDL cholesterol (r=0.345 and 0.279, respectively; P<0.01) and a negative correlation with HDL cholesterol (r=-0.265 and -0.338, respectively; P<0.02) in FH mutation carriers. In FH without molecular diagnosis, AT thickness and breadth also corre-
lated with LDL cholesterol (r=0.368 and 0.583, respectively; P<0.02) but not with HDL cholesterol. In either FH group or in FCH subjects, apo E genotypes were unrelated to AT variables.

AT thickness of the 29 FH subjects with a history of CHD (6.9±3.2 mm) was significantly (P=0.030) higher than corresponding values of the 97 asymptomatic individuals (5.7±2.4 mm). These differences persisted (P=0.034) after adjustment for sex, age, weight, and LDL cholesterol (7.0±2.6 versus 5.7±2.5 mm, respectively).

### Tendon Thickness Thresholds for the Diagnosis of FH

As quantitative AT measures variably overlapped between FH and non-FH subjects (Table 2), ROC curves were used to determine sex- and age-specific threshold values for the diagnosis of FH. Because the ROC curves representing AT thickness and breadth were essentially superimposed, only the cutoff points of thickness are shown for both men and women above and below the median age of FH mutation carriers (Table 3). As seen by the areas under the curves, the ROC curves performed better in older individuals. Because the pretest probability in FH is generally low (1 in 500), cutoffs with high specificity were sought to avoid false-positive results, aggressive treatment of unaffected individuals, and undue concern for family members. These thresholds correspond to percentiles 81 to 92 of the distribution of AT thickness in pooled non-FH subjects. Use of these cutoffs classified as FH 19 of the 46 subjects (41%) with a clinical diagnosis of FH but no identified genetic defect.

The Figure shows scatter plots of AT thickness in men and women against age. The majority of non-FH subjects show values below threshold lines, indicating the high specificity of these cutoffs. The values of younger FH subjects, both genetically confirmed and with no identified mutation, scatter widely above and below the threshold lines, whereas those of older subjects predominate above the lines, pointing to higher threshold sensitivity in the latter. In men, but not in women, the proportion of subjects with markedly enlarged tendons falls abruptly after age 60. A likely explanation is poor survival of FH men with more severe clinical phenotypes.

### Concordance between Clinical Examination and Sonography

Table 4 shows the concordance between clinical examination and sonography in the diagnosis of AT xanthomas. Whereas a small proportion of tendons felt to be enlarged by the clinicians were sonographically normal, an abnormal sonogram by any of the 2 criteria of thickness above cutoff values or abnormal echostructure was found in 68% of FH mutation carriers and 46% of FH subjects without DNA diagnosis, thus increasing the diagnostic rates of physical examination by ≈25% in both groups. Sonographic xanthomas in normalized ATs were found in 10 of the 127 FH subjects.

### Validation Sets for Thickness Thresholds

Application of cutoff values to a series of 70 FH mutation carriers from Zaragoza (Table 1) who were assessed for AT thickness with the same sonographic criteria correctly classified FH in 56 (80%) of them. When using these thresholds in another set of 58 dyslipidemic, non-FH subjects studied in the same way in Zaragoza, 53 (88%) were correctly classified as non-FH.

### Discussion

The results of this study show that sonographic AT features improve on the clinical diagnosis of xanthomas, are normal in

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Area Under the Curve</th>
<th>95% CI</th>
<th>Tendon Thickness Threshold, mm</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men ≤45 years</td>
<td>0.65</td>
<td>0.51–0.78</td>
<td>5.3</td>
<td>49%</td>
<td>91%</td>
</tr>
<tr>
<td>Men &gt;45 years</td>
<td>0.84</td>
<td>0.70–0.98</td>
<td>5.7</td>
<td>75%</td>
<td>89%</td>
</tr>
<tr>
<td>Women ≤50 years</td>
<td>0.76</td>
<td>0.62–0.89</td>
<td>4.8</td>
<td>50%</td>
<td>88%</td>
</tr>
<tr>
<td>Women &gt;50 years</td>
<td>0.79</td>
<td>0.67–0.91</td>
<td>4.9</td>
<td>67%</td>
<td>81%</td>
</tr>
</tbody>
</table>
Men had ATs that were thicker and larger than those of women in all of the groups. These gender differences have been observed in other studies\(^{11,14,16,26}\) and may be explained by the usually higher musculoskeletal development in men. Supporting prior results in control subjects,\(^{26}\) AT size was related to body weight, a plausible finding given the body support function that AT plays in skeletal physiology. In FH, but not in controls or non-FH subjects, AT size correlated positively with LDL cholesterol and negatively with HDL cholesterol. This indicates that the severity of the lipid phenotype influences extravascular cholesterol deposition only in FH. The presence of hypercholesterolemia during childhood,\(^{1–3}\) when tendons are growing, is a unique feature of FH that may explain these findings.

The AT thickness thresholds for diagnosing FH that we derived from ROC curves are similar to those found by Descamps et al\(^{16}\) in a like series of FH with DNA diagnosis from Belgium. These authors proposed a single cutoff point of 5.8 mm with 75% sensitivity and 85% specificity. To avoid false-positive results in a genetic disorder like FH with a low a priori probability in the population,\(^{23}\) we sought sex- and age-specific discriminatory thresholds that are less sensitive in young subjects but more specific at all ages (Table 3). When available, DNA diagnosis is clearly more sensitive,\(^{1–3}\) as shown in the present series, where 1 of every 3 FH mutation carriers had sonographically normal AT by any criteria (Table 4). The cutoff values performed well in validation sets of FH and non-FH individuals with genetic testing, clinical diagnoses, and AT sonograms obtained with a similar protocol, thus supporting their wider applicability, at least in a population like the Spanish one, where FH is genetically heterogeneous.\(^{17}\)

Compared with molecularly defined FH subjects, those with clinical FH and no DNA diagnosis had a milder lipid phenotype but similar clinical severity. Application of AT thickness thresholds to these individuals classified 41% of them as FH, emphasizing the uncertainty of the group’s categorization.\(^{24}\) Future refinements of molecular testing should clarify diagnoses in this ill-defined group of clinically severe hypercholesterolemias.

As reviewed recently,\(^{27}\) other imaging techniques may be used to accurately measure AT size, although none can depict xanthomas. Because sonography is a safe, low-cost, rapid, and reliable procedure, its use for the assessment of both AT size and echostructure represents a valid and practical alternative for uncovering both enlarged tendons and xanthomas that noticeably increase the yield of physical examination. The fact that the sonographic AT characteristics are normal in non-FH dyslipidemias is an added value when using this technique in the differential diagnosis of FH.

### Acknowledgments

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### Table 4. Concordance between Physical Examination and Sonography in the Diagnosis of AT Xanthomas

<table>
<thead>
<tr>
<th>Subjects with FH</th>
<th>Physical Examination</th>
<th>Sonographic Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
<td>Xanthoma*</td>
</tr>
<tr>
<td>Molecularly defined</td>
<td>23</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>26 (52%)</td>
<td>55 (68%)</td>
</tr>
<tr>
<td>No identified mutation</td>
<td>23</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>25 (54%)</td>
<td>21 (46%)</td>
</tr>
</tbody>
</table>

*Defined as tendons with abnormal echostructure and/or thickness above threshold values for diagnosis of FH.
References


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**Figure I:** Saggital sonograms of Achilles tendons. a: Normal tendon thickness (4.6 mm), showing homogeneous fibrillar echostructure. b: Enlarged tendon (8 mm) with loss of fibrillar structure in the outer layers (xanthoma) and preserved structure in the inner layers. c: Markedly enlarged xanthomatous tendon (15.9 mm) with loss of fibrillar structure throughout and a sonolucent area of local cholesterol deposition (arrows).