Tendon Xanthomas in Familial Hypercholesterolemia Are Associated With Cardiovascular Risk Independently of the Low-Density Lipoprotein Receptor Gene Mutation

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Objective—To investigate the significance of tendon xanthomas (TX) in heterozygous subjects with familial hypercholesterolemia (hFH).

Methods and Results—951 men and women with genetic diagnosis of hFH were studied, of whom 278 (29.2%) presented TX. TX frequency increased with age from 6.9% in subjects 20 to 30 years to 38.3% at 51 to 60 years, with a decrease in those older than 60 years. Total and low-density lipoprotein (LDL) cholesterol were higher in TX+ than in TX− subjects (439.0±78.5 mg/dL and 363.1±76.5 mg/dL versus 400.6±73.4 and 323.3±71.0, respectively; \( P=0.001 \)). High-density lipoprotein (HDL) cholesterol was lower in TX+ than in TX− subjects (50.4±15.0 mg/dL versus 53.1±14.8 mg/dL; \( P=0.005 \)). Lp(a), apolipoprotein E genotype, and type of LDL receptor gene mutation showed no differences between groups. 102 TX+ reported premature cardiovascular disease (CVD) (36.7%) versus 93 TX− (13.8%) (\( P=0.001 \)). The relative odds for premature CVD were higher in women (4.49 versus 2.26), and increased in hFH younger than 51 years to 3.60 (95% CI, 1.703 to 7.608) in men and to 17.1 (95% CI, 2.697 to 108.920) in women. In the multivariate analysis, age, male sex, LDL cholesterol, and hypertension showed significant positive association with TX, whereas body mass index showed negative association with TX.

Conclusions—TX are associated with cardiovascular risk factors and higher CVD, indicating that their detection indicates the need for more aggressive lipid-lowering intervention. (Arterioscler Thromb Vasc Biol. 2005;25:1960-1965.)

Key Words: cardiovascular disease ■ familial hypercholesterolemia ■ xanthomas

Familial hypercholesterolemia (FH) is a genetic disorder of lipoprotein metabolism characterized by very high plasma concentrations of low-density lipoprotein (LDL) cholesterol, deposition of cholesterol in extravascular tissues, such as tendon xanthomas (TX), and increased risk of premature coronary heart disease (CHD).1 FH is a common autosomal codominant disease caused by defects in the low-density lipoprotein receptor (LDLR) gene.2 In heterozygous FH patients, the clinical expression of FH is highly variable in terms of the severity of hypercholesterolemia, the presence of TX, and the age of onset and severity of CHD, even in subjects sharing the same LDLR gene defect.3,4

TX are highly specific for FH in subjects with genetic high LDL cholesterol, and current recommendations include them as an important clinical diagnostic criterion.5 TX are composed of monocyte-derived foam cells resulting from intracellular accumulation of lipids and connective tissue.6

Approximately 30% to 50% of heterozygous FH (hFH) patients with genetic diagnosis have TX.3,4,7 The mechanism by which some subjects with hFH have develop TX and others do not, even while disclosing similar plasma LDL cholesterol levels and sharing the same LDLR gene mutation, is unknown.4 A previous report has suggested that the appearance of xanthomas in hFH is controlled by a second gene distinct from the LDLR gene, as yet not identified.8

The clinical significance of TX presentation heterogeneity has not been fully established. Because of the lipid and cellular similarities between TX and atherosclerotic plaques, it is conceivable that hFH subjects in whom TX develops could also have a higher predisposition to atherosclerosis. In fact, the presence of TX has been associated with very premature CHD,9 although a recent report from the Simon Broome register in the United Kingdom showed a similar CHD risk among patients with and without TX.10 However,
in both studies the diagnosis of hFH was based on clinical criteria, in which both TX and CHD play an important diagnostic role that could obscure interpretation of the results.

The Spanish FH register offers a good opportunity to explore the clinical meaning of TX.11 In the register, >2000 nonrelated probands from lipid clinics all over Spain with clinical suspicion of FH have been included, and >200 different mutations have been identified.11 Additionally, a rapid genetic micro-array–based test has been developed, permitting the genetic diagnosis of >1200 patients to date.12

Materials and Methods

Subjects

Subjects were selected from the Spanish FH register, supported by the “Fundación Española Hipercolesterolemia Familiar.” The main characteristics of the register have been previously reported.11,12 In summary, a total of 77 lipid clinics throughout Spain recruited FH patients with the same clinical criteria. To homogenize criteria, all participants attended at least 3 different meetings specially oriented toward clinical diagnosis, including the physical examination of TX. hFH subjects were considered positive for cardiovascular disease (CVD) if they had a documented history of myocardial infarction, coronary artery bypass graft surgery, percutaneous transluminal coronary angioplasty, angina pectoris with angiographically coronary atherosclerosis (>50% stenosis), ischemic atherothrombotic stroke, or chronic arterial peripheral vascular disease. Premature CVD was considered if the first event occurred before age 56 in men and before age 66 in women. TX were clinically examined for at the local lipid clinics by inspection and palpation of tendons and were considered if the Achilles tendons appeared diffusely enlarged or if the Achilles tendons or extensor tendons of the hands were deformed by one or more focal nodularities.

All subjects with TX were clinically diagnosed of hFH caused by functional mutations in the LDLR gene were selected for this study. Identification of mutations in Spain has been performed for our group in the past 10 years.11,12 Of these, all hFH with TX (TX+) (n=278, 138 women and 140 men) and all genetically diagnosed hFH without TX (TX-) older than 22 years (n=673 375 women and 298 men) were selected. This age cutoff point in the TX+ group was established because it was the age of the youngest TX+ hFH subject.

Mutations in the LDLR gene causing FH were classified, when possible, as receptor-defective or receptor-negative on the basis of the residual LDLR activity found in previously reported cultured cells with homozygous LDLR mutation (>5% for receptor defective and <5% for receptor negative).4 Mutations leading to a frame-shift and a truncated receptor were also considered as receptor-negative.4 All participants gave written informed consent and the protocol was approved by the local ethics committees.

Lipid Concentrations

Baseline out-of-treatment values for total cholesterol, triglycerides, and HDL cholesterol were provided in the clinical data set by the participating lipid clinics. Laboratory methods were standardized among lipid clinics. All the laboratories are participants in the standardization protocols developed by the Spanish Society of Clinical Biochemistry with coefficient of variation for cholesterol <3%.

Lipoprotein A

Lipoprotein a [Lp(a)] was determined in the central laboratory from fasting samples sent by the lipid clinics. Serum concentrations of Lp(a) were measured using kinetic immunonephelometry with polyclonal antibodies (Beckman).

Apolipoprotein E Genotyping

DNA was isolated from peripheral blood cells with the method of Miller et al.13 DNA was quantified and diluted to a final concentra-

Figure 1. Percentage of hFH subjects with tendon xanthomas by deciles of age.

Results

Frequency of TX in Heterozygous Subjects

With FH

TX were clinically detected in 278 (29.2%) subjects. The frequency of TX was slightly higher in men (32.0%) than in women (26.9%), but this difference was not statistically significant (P=0.087). A clear relationship of TX with age was evident in men and in women (Figure 1). TX were rare in those younger than 30 years, and their frequency increased throughout life by ≈10% for each decade in both sexes. Interestingly, the proportion of hFH with TX did not increase but in fact decreased in subjects older than 60 years in both sexes, probably indicating a poorer survival rate in subjects with TX.

Characteristics Associated With the Presence of TX

Table 1 shows the clinical variables analyzed in the study. Subjects with TX (TX+) were significantly older (54.0±11.9 years versus 49.4±14.2 years; P=0.01) than those without TX (TX-). There were no differences in the distribution of smoking habits between TX+ and TX- subjects. Because many subjects were former smokers, especially the men, we calculated the level of cigarette consumption from the number of cigarettes consumed per day and the number of years smoking (cigarettes/day×years). TX+ men showed an almost significant trend to higher consumption than TX- men (269.8±300.8 versus 203.4±227.2; P=0.060). CVD was more prevalent among TX+ subjects in both sexes, but the age of the first event was only different in women. TX+ women reported their first CVD event 4.6 years earlier than TX-
women (54.6±10.9 versus 50.0±10.3; *P*=0.041). The reported history of hypertension and the mean systolic and diastolic blood pressure were significantly higher in TX+ than in TX− subjects (Table 1).

Total cholesterol and LDL cholesterol concentrations were ∼40 mg/dL higher in TX+ than in the TX− (439.0±78.5 mg/dL and 363.1±76.5 mg/dL versus 400.6±73.4 and 323.3±71.0, respectively; *P*=0.001 in both cases). The differences in total and LDL cholesterol were consistently found in both sexes (Table 1). HDL cholesterol was lower in TX+ than in TX− (50.4±15.0 versus 53.1±14.8; *P*=0.005), but this difference was because of the higher HDL cholesterol concentration and the lower incidence of TX in women than in men, in that HDL cholesterol concentrations did not differ in TX− and in TX+ when the sexes were studied separately.

Lp(a) was higher in TX+ in men and in women, but the differences were slight and did not reach statistical significance (50.9±51.9 mg/dL versus 43.4±45.9 mg/dL, *P*=0.061).

**Tendon Xanthomas and ApoE Genotype**

The apoE genotype was analyzed in 681 (71.6%) subjects of the total sample, 230 TX+ (82.7%) and 451 TX− (67.0%). ApoE genotype distribution and apoE3, apoE4, and apoE2 allele frequencies were similar to those previously reported in the Spanish general population. There was a nonsignificant trend toward a higher frequency of apoE4 allele–containing genotypes among TX+ subjects (Table 2); this did not change when only E4/4 and E4/3 were compared with E3/3 subjects.

**TX, Lipid Levels, and LDLR Gene Mutations**

A total of 224 different mutations in the LDLR gene were responsible for hFH in the total group. The genetic defects included 206 different point mutations and 18 different large rearrangements in the LDLR gene. LDLR mutation could be classified in 677 cases as defective or negative according to the previously reported receptor residual activity “in vitro.” In the remaining 274 patients, most with previously unreported mis-sense mutations and mutations affecting splicing, LDLR residual activity was unknown. No differences were found in the distribution of the type of the LDLR mutation and the presence of TX (Table 3). TX+ men and women with defective LDLR mutations and men with unclassified mutations had lower LDL cholesterol concentrations than men and women with negative LDLR mutations. This difference was not observed in TX− subjects (Table 3).

**Tendon Xanthomas and CVD**

Premature CVD was present more frequently in TX+ than in TX−. A total of 102 TX+ reported premature CVD (36.7%)
Multivariate Analysis

Multiple logistic regression analyses were performed with the presence of xanthomas as dependent variable, and LDL cholesterol, HDL cholesterol, triglycerides, body mass index, age, sex, cigarette consumption, family and personal history of premature CVD, hypertension, diabetes, apoE genotype, and the type of mutation in the LDLR gene as independent variables. ApoE genotype and the type of mutation in the LDLR were found not to be significantly associated with TX in the multiple logistic regression analysis and were taken out in further analyses to avoid missing values.

The multivariate analysis was performed with the whole population and with men and women younger than 51 years of age. LDL cholesterol and premature CVD were found to be significantly associated with TX (Table 4). When the analysis was performed by sex, age in men and TG in women were also significantly associated with TX. Although LDL cholesterol and premature CVD were the main associated variables in both sexes, the relative odds for premature CVD were higher in women (4.49 versus 2.26) than in men. This odds ratio increased when subjects younger than 51 years were considered, and increased to 3.60 (95% CI, 1.703 to 7.608) in men and to 17.1 (95% CI, 2.697 to 108.920) in women. It is noteworthy that all CVD classic risk factors disappeared, except LDL cholesterol, when premature CVD was present in

### Table 2: Apolipoprotein E Genotype Distribution Relative to the Presence of Tendon Xanthomas

<table>
<thead>
<tr>
<th>Genotype</th>
<th>TX⁺, n (%)</th>
<th>TX⁻, n (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E3/3</td>
<td>85 (73.9)</td>
<td>147 (78.6)</td>
<td></td>
</tr>
<tr>
<td>E2</td>
<td>6 (5.2)</td>
<td>6 (3.2)</td>
<td></td>
</tr>
<tr>
<td>E4</td>
<td>23 (20.0)</td>
<td>33 (17.6)</td>
<td></td>
</tr>
<tr>
<td>E2/4</td>
<td>1 (0.87)</td>
<td>1 (0.53)</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E3/3</td>
<td>80 (69.6)</td>
<td>197 (74.6)</td>
<td></td>
</tr>
<tr>
<td>E2</td>
<td>4 (3.5)</td>
<td>18 (6.6)</td>
<td></td>
</tr>
<tr>
<td>E4</td>
<td>30 (26.1)</td>
<td>46 (17.4)</td>
<td></td>
</tr>
<tr>
<td>E2/4</td>
<td>1 (0.87)</td>
<td>3 (1.1)</td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>165 (71.7)</td>
<td>344 (76.3)</td>
<td>0.375</td>
</tr>
</tbody>
</table>

*a*Apolipoprotein E genotype was determined in 681 subjects (230 TX⁺ and in 451 subjects TX⁻).

**Table 3: Presence of Tendon Xanthomas and Lipid Levels Relative to the Type of Mutation in the LDLR Gene**

<table>
<thead>
<tr>
<th></th>
<th>Defective</th>
<th>Negative</th>
<th>Unclassified</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX⁺, n (%)</td>
<td>42 (30.0)</td>
<td>50 (35.7)</td>
<td>48 (34.3)</td>
</tr>
<tr>
<td>LDLc, mg/dL</td>
<td>350.2±59.1</td>
<td>362.9±74.7</td>
<td>363.1±66.6</td>
</tr>
<tr>
<td>HDLc, mg/dL</td>
<td>44.4±12.8</td>
<td>44.5±9.88</td>
<td>46.4±12.6</td>
</tr>
<tr>
<td>TG, mg/dL</td>
<td>115.7±43.5</td>
<td>161.3±139.2*</td>
<td>135.1±56.0</td>
</tr>
<tr>
<td>TX⁻, n (%)</td>
<td>105 (35.2)</td>
<td>120 (40.3)</td>
<td>73 (24.5)</td>
</tr>
<tr>
<td>LDLc, mg/dL</td>
<td>300.5±61.2</td>
<td>324.0±81.4*</td>
<td>335.0±63.2†</td>
</tr>
<tr>
<td>HDLc, mg/dL</td>
<td>47.4±13.5</td>
<td>47.4±13.7</td>
<td>49.8±15.3</td>
</tr>
<tr>
<td>TG, mg/dL</td>
<td>128.0±71.6</td>
<td>133.9±87.4</td>
<td>119.7±43.8</td>
</tr>
</tbody>
</table>

Quantitative values are mean±SD.

TG indicates triglycerides.

*P<0.05 negative vs defective; †P<0.01 unclassified vs defective.

P denotes the significance of t test considering the type of LDLR mutation.
The frequency of TX in our register was aged 23 years, and when clinically frequent at early ages; in fact, the youngest hFH subject with premature CVD, hypertension, diabetes, total cholesterol, triglycerides, LDL cholesterol, HDL cholesterol, and Lp(a). Therefore, we analyzed the multivariate analysis, removing premature CVD from the model. As a result, traditional risk factors such as age, sex, LDL cholesterol, triglycerides, LDL cholesterol, HDL cholesterol, and Lp(a). The variables included in the model for association with the presence of TX included age, sex, BMI, smoking status, cigarette consumption, family and personal history of premature CVD, hypertension, diabetes, total cholesterol, triglycerides, LDL cholesterol, HDL cholesterol, and Lp(a).

**TABLE 4. Multiple Logistic Regression Analysis for Presence of Tendon Xanthomas in Heterozygous Subjects With Familial Hypercholesterolemia**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entire group†</td>
<td>LDL cholesterol</td>
<td>1.0067</td>
<td>1.005–1.009</td>
</tr>
<tr>
<td>Men</td>
<td>Age</td>
<td>1.0223</td>
<td>1.004–1.041</td>
</tr>
<tr>
<td>Women</td>
<td>LDL cholesterol</td>
<td>1.0081</td>
<td>1.005–1.011</td>
</tr>
<tr>
<td></td>
<td>Premature CVD</td>
<td>2.2597</td>
<td>1.404–3.637</td>
</tr>
<tr>
<td></td>
<td>Triglycerides</td>
<td>0.9922</td>
<td>0.987–0.997</td>
</tr>
<tr>
<td>Entire group‡</td>
<td>LDL cholesterol</td>
<td>1.007</td>
<td>1.005–1.009</td>
</tr>
<tr>
<td></td>
<td>Sex (women)</td>
<td>0.614</td>
<td>0.451–0.838</td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>1.018</td>
<td>1.006–1.031</td>
</tr>
<tr>
<td></td>
<td>BMI</td>
<td>0.954</td>
<td>0.917–0.991</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
<td>1.535</td>
<td>1.015–2.320</td>
</tr>
</tbody>
</table>

The importance of TX has been traditionally limited to clinical diagnosis of FH. TX has been used as a key feature for the diagnosis of FH worldwide. However, TX are not frequent at early ages; in fact, the youngest hFH subject with TX in our register was aged 23 years, and when clinically detected the frequency of TX is, approximately, one-third that of the subjects with genetic diagnosis (Figure 1). Therefore, sensitivity of TX is quite low for diagnosis of FH, especially in the case of younger relatives. The frequency of TX in hFH varies greatly among studies. This can probably be explained by the different mean ages of the subjects in the various studies, the methods of detection of TX used, and the criteria used for the diagnosis of FH. As one would expect, in those studies in which TX are a major clinical criterion the frequency of detection tends to be higher. In 2 previously published studies with genetically based diagnoses, the frequency of TX was 29% and 33.1%, quite similar to that obtained in our study. Ultrasonography accurately quantifies tendon thickness, which is enlarged when xanthomas are present. Because the Achilles tendon is the most common location for xanthomas to develop, ultrasonography of the Achilles tendon has been demonstrated to increase sensitivity up to 75%, with, however, a probable loss of specificity regarding other forms of hypercholesterolemia.

The mechanism of production of TX is not known. It is clear that several decades of very high LDL cholesterol in blood are needed in most cases for their formation, but some other factors must be involved, because not all hFH have TX develop, and some other forms of hypercholesterolemia, such as familial combined hyperlipidemia, also usually produce very high levels of LDL cholesterol for many years and TX never develops. One factor that might be involved is the presence of hypercholesterolemia during childhood when tendons are growing. Another possibility is that enhanced mechanical stress caused by higher levels of exercise in TX+ than in TX− subjects is involved in TX development. Unfortunately, a physical activity questionnaire was not included in the study.

Vergopoulos et al, studying the transmission of TX in a large Syrian kindred with FH, have described how TX in that family were probably caused by an unknown autosomal gene, distinct from LDLR. Several rare genetic diseases other than hypercholesterolemia produce TX, including cerebrotendinous xanthomatosis and sitosterolemia. Cerebrotendinous xanthomatosis is a rare autosomal recessive disease brought on by cholestanol accumulation in the brain, lens, and tendons of affected subjects; it is caused by mutations in sterol 27-hydroxylase (CYP27) gene. Sirotosterolemia is also caused by accumulation of another noncholesterol sterol, sitosterol, caused by mutations in the ABCG5 or ABCG8 genes. Although the possible contribution of these genes to the development of TX in FH has not been explored, normal concentrations of both cholestanol and sitosterol have been reported in hFH. Despite this, the question of plant sterol and other noncholesterol sterol in hFH subjects both with and without TX requires further attention.

Several conclusions may be drawn from our study about the mechanism of production of TX. First, as one would expect, because of the histological similarities between TX and atherosclerotic vascular lesions, TX are associated with traditional cardiovascular risk factors such as age, male sex, higher blood pressure, and higher LDL cholesterol concentrations. We could not find any association between TX and the apolipoprotein E genotype, in accord with what we have previously demonstrated for CVD, nor with tobacco consumption even when the total amount consumed was considered. Second, the type of mutation in the LDLR gene is not an important factor associated with the presence of TX. FH is genetically heterogeneous in Spain, with >200 different mutations discovered so far. For this reason, the only possible approach was to classify the mutations as defective or null alleles when it was possible to do so. Negative alleles are usually associated with higher LDL cholesterol concentrations, but LDL cholesterol variation in hFH is caused by multiple environmental and polygenic factors, and when adjusted for LDL cholesterol, the type of mutation does not explain the presence of TX.

The most important finding of our study is the strong independent association found between the presence of TX and premature CVD. Men and women showed an increased risk when TX were detected during clinical examination. This was even more impressive in women, among whom premature CVD disease is not often seen even among hFH, but it is
very high in women with TX. Among the 15 women in whom CVD developed before age 50 year, 10 had TX, which means the odds ratio is 17.1 ($P<0.0001$) (Figure 2). This has evident clinical implications, and TX must be seen as not only a diagnostic tool for FH but also, and more importantly, a prognostic factor, which should suggest a more aggressive approach to treatment for this subgroup of hFH subjects—something that has not previously been considered.8

One previous study has analyzed the clinical implication of TX in FH. The Simon Broome Register in UK recently published similar CHD mortality in subjects with and without TX,10 in clear contrast to our results. However, important differences in the inclusion criteria between the 2 studies may explain this discrepancy. In our study, suspected FH subjects were included because high total cholesterol concentration and genetic confirmation were required; thus, only patients with definitive and highly specific diagnoses were analyzed. In the Simon Broome Register, the diagnosis of FH was based on 2 possibilities: (1) hypercholesterolemia plus TX or (2) hypercholesterolemia plus personal or familiar history of premature myocardial infarction. As the authors pointed out, TX subjects in their study could be easily misclassified as FH and, in fact, the LDLR mutation detection rate for this group of TX patients is low (14% to 18%), much lower than in the TX+ patient group (32% to 79%).10

In summary, in this large group of genetically defined hFH adult subjects, TX were present in 29.2% of cases. The frequency increased with age until 60 years, and decreased after this, probably indicating a poor survival associated with TX. Subjects with TX were older and had higher systolic blood pressure, total cholesterol, and LDL cholesterol; they were more frequently men than women. Most importantly, there was a greater presence of premature CVD in subjects with TX, indicating that their clinical detection implies a higher cardiovascular risk that requires a more aggressive lipid-lowering intervention.

Acknowledgments

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References

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