JIM Research Letter

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Achilles tendon ultrasonography in familial hypercholesterolemia: A sub-study of the LIpid transPort disorders Italian GEnetic Network (LIPIGEN)

Dear Editor,

Familial hypercholesterolemia (FH) is a common genetic disease due to mutations causing lifelong exposure to elevated low-density lipoprotein cholesterol (LDL-C) levels, a causal factor for premature occurrence of atherosclerotic cardiovascular disease (ASCVD) [1, 2]. The clinical diagnosis of FH principally relies on clinical algorithms, such as the Dutch Lipid Clinic Network (DLCN) criteria (considering personal and family history of high LDL-C, premature ASCVD, premature corneal arcus, and tendon xanthomata) and can be confirmed by genetic testing [3]. However, DLCN diagnostic performance is far from optimal [4], with the physical analysis of Achilles tendon xanthomata representing a critical point [5], not only because of the interoperator variability [6], but also because xanthomata are not always easily detectable. Achilles tendon ultrasonography represents a safe, reproducible, and inexpensive alternative technique [7] that allows physicians to identify either focal lesions or diffuse changes in tendon echotexture and to measure calcaneal tendon thickness [8]. Here we aimed to evaluate the ability of Achilles tendon ultrasonography in the clinical and genetic classification of subjects with FH, taking advantage of data from five centers belonging to the established LIpid transPort disorders Italian GEnetic Network (LIPIGEN [9], see Supplementary Material for all methodological information).

We evaluated 769 adults with a clinical diagnosis of FH. Seventy-five subjects (9.8%) presented with clinically detected xanthomata, and 255 subjects (33.2%) presented with xanthomata detected by ultrasound analysis. Therefore, 180 subjects presented with xanthomata only detected by ultrasound that could not have been identified by clinical examination (Table S1). This latter group showed pretreatment LDL-C levels lower than those of subjects with clinically detected xanthomata (300.5 ± 78.5 vs 347.6 ± 85.3 mg/dL, $p < 0.0001$) but significantly higher than those of subjects without xanthomata (254.4 ± 63.4 mg/dL, $p < 0.0001$), and lower prevalence of early cardiovascular events than that of subjects with clinically detected xanthomata (13.3% vs 24.0%, $p = 0.04$) but higher compared to subjects without xanthomata (13.3% vs 7.8%, $p < 0.0001$).

Considering xanthomata detected by ultrasound analysis instead of clinically detected xanthomata in the DLCN score calculation, the performance of the DLCN score increased from 61.8% to 65.7% with the cut-off at 6 points (probable diagnosis), and from 32.5% to 43.2% with the cut-off at 9 points (definite diagnosis) (Fig. 1). Among definite FH subjects, the prevalence of clinically detected xanthomata and of xanthomata detected by ultrasound analysis was 30.0% and 67.6%, respectively.

The ultrasound evaluation also showed a higher concordance with the genetic diagnosis; in the whole cohort, the number of subjects with xanthomata and monogenic FH increased from 9.4% to 31.5% using ultrasound instead of clinical detection (Table S2).

Finally, we found that maximum Achilles tendon thickness (higher in subjects with clinically detected xanthomata vs those with xanthomata detected only by ultrasound analysis) positively correlated to the LDL-C burden in subjects with positive genetic diagnoses, but not in those with negative genetic tests (Figure S1, panels A, B, and C). However, the measurement of Achilles tendon thickness demonstrated poor sensitivity both for identifying subjects with clinically defined FH as well as subjects with genetic confirmation of the FH phenotype (Table S3; Figure S2, panels A and B).

In line with previous monocentric studies [10], our findings support that ultrasonography improves

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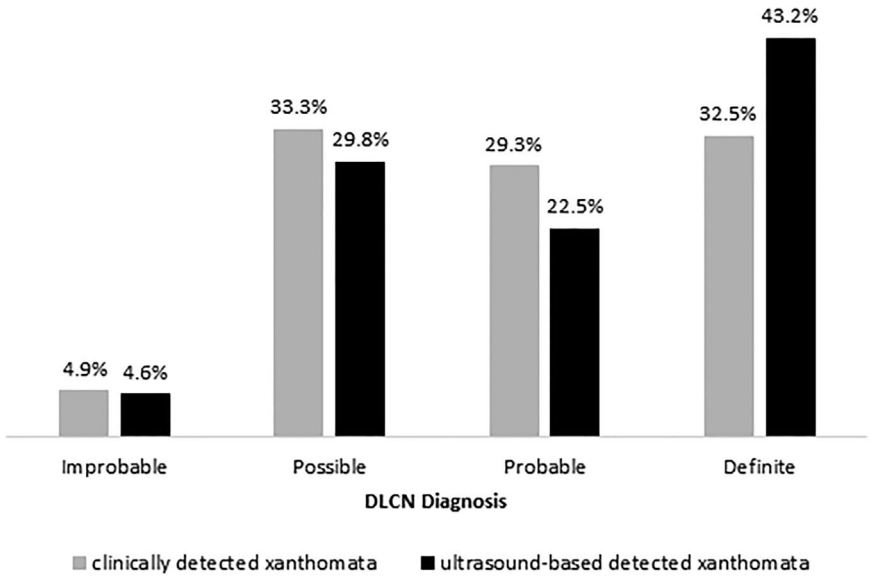

Fig. 1 *Reclassification of Dutch Lipid Clinic Network (DLCN) categories by ultrasound-based analysis of Achilles tendon xanthomata.*

the diagnosis of monogenic forms of FH. Therefore, ultrasonography represents an additional opportunity for the physician to detect FH patients when the genetic test is not available, since the prevalence of xanthomata only detected by ultrasound was significantly higher in FH/M+ versus FH/M−, even stratifying for LDL-C levels (not shown). This finding also supports that ultrasonography could allow for the identification of FH subjects with more severe phenotypes secondary to a lifetime exposure to elevated LDL-C, underscoring the possible prognostic value of this clinical tool. The variability of this technique, however, does not allow for drawing firm indications on the values at which Achilles tendon ultrasonography identifies tendon xanthomata, and limits its universal use for FH diagnosis unless a reference value is established in each center [7]. However, the real-life setting from which we collected data decided to standardize its activity on the grounds that a shared protocol might serve as a proof-of-concept of ultrasound as an additional tool to identify FH patients at higher ACVD risk. The approach will eventually help to increase the sensitivity of physicians, general practitioners, and healthcare providers towards early and effective preventive LDL-C lowering interventions. In conclusion, ultrasonography identifies patients with tendon xanthomata that cannot be detected by physical examination, improving the number of patients correctly identified as definite FH according to the DLCN score and those with proven genetic mutations.

Conflict of interest

The authors do not report any conflict of interest related to this work.

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