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Achilles tendon ultrasonography in the clinical screening of familial hypercholesterolaemia – a cross-sectional analysis

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Summary

BACKGROUND AND AIMS: People with familial hypercholesterolaemia are 13 times more likely to develop cardiovascular disease than the general population. However, familial hypercholesterolaemia remains largely underdiagnosed. Tendon xanthoma is a specific clinical feature of familial hypercholesterolaemia and its presence alone implies a probable diagnosis of familial hypercholesterolaemia according to the Dutch Lipid Clinic Network Score (DLCNS). The aim of the study was to determine whether ultrasound detects more Achilles tendon xanthomas (ATX) than clinical examination.

METHODS: We recruited 100 consecutive patients with LDL-C ≥4 mmol/l. Achilles tendons were evaluated through clinical examination by trained physicians and sonographic examination by another physician blind to the results of clinical examination. Blind second readings of ultrasound images were performed by an expert in musculoskeletal ultrasound. We compared the proportion of patients with ATX detected by either clinical examination or ultrasound and the proportion of patients with a probable/definite familial hypercholesterolaemia diagnosis on the DLCNS before and after ultrasound.

RESULTS: Mean (SD) age was 47 (12) years; mean highest LDL-C was 6.57 mmol/l (2.2). ATX were detected in 23% of patients by clinical examination and in 60% by ultrasound. In consequence, 43% had a probable/definite diagnosis of familial hypercholesterolaemia on the DLCNS using clinical examination compared with 72% when ultrasound was used.

CONCLUSION: Compared to clinical examination, ultrasound examination of the Achilles tendon substantially improves the detection of ATX and may help to better identify patients with familial hypercholesterolaemia who are at high risk for premature cardiovascular disease.

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Introduction

Familial hypercholesterolaemia is the most common autosomal dominant genetic disease, with an estimated prevalence of 0.3–0.5% for heterozygous familial hypercholesterolaemia [1–3]. It is characterised by high levels of low-density lipoprotein cholesterol (LDL-C) in blood and cholesterol depositions in tendons. Familial hypercholesterolaemia is severely underdiagnosed: fewer than 1% of people with familial hypercholesterolaemia have been diagnosed in many countries worldwide; the figure for Switzerland is 13% [4]. Most familial hypercholesterolaemia cases (~79%) are caused by mutations in the LDL receptor (*LDLR*) gene. Mutations in the apolipoprotein B (*APOB*) gene account for ~5% and mutations in the proprotein convertase subtilisin/kexin type 9 (*PCSK9*) gene for <1% of familial hypercholesterolaemia cases. The remaining ~15% of familial hypercholesterolaemia cases are either polygenic or caused by unknown mutations [5, 6]. If untreated, people with familial hypercholesterolaemia have up to 13 times higher risk of premature cardiovascular disease than the general population [4, 7]. Untreated men have a 50% risk of a coronary event by the time they are 50; untreated women have a 30% risk by the time they are 60 [8]. Therefore, early diagnosis and treatment are essential and can substantially reduce cardiovascular risk in individuals with familial hypercholesterolaemia [9–12].

The diagnosis of familial hypercholesterolaemia is based on clinical and laboratory findings, with or without genetic testing. Ideally, genetic testing should be done [13], but it is not reimbursed in many countries (e.g. not reimbursed in Switzerland). However, failure to find a mutation does not necessarily exclude a diagnosis of familial hypercholesterolaemia, as genetic testing may miss 20–40% of patients categorised with “definite” familial hypercholesterolaemia according to the clinical diagnostic criteria. Negative genetic test results may be due to insufficient sensitivity of the methods used (e.g. next-generation sequencing finds more pathogenic genes than limited-variant screening) or to the presence of mutations in genes that remain unknown [14–18].

Clinical findings are typically scored using systems such as the Dutch Lipid Clinic Network Score (DLCNS) [4]. DLCNS consists of family history (first-degree relative with premature cardiovascular disease, LDL-C ≥5 mmol/l, tendon xanthoma or corneal arcus), clinical history (personal history of premature cardiovascular disease), tendon xan-

thoma or corneal arcus on physical examination, LDL-C level and presence of a familial hypercholesterolaemia mutation on DNA analysis. A diagnosis of familial hypercholesterolaemia is considered definite if the total DLCNS is greater than 8, probable if it is 6–8, possible if 3–5 and unlikely if the score is under 3 [1, 19].

Xanthomas are localised lipid deposits in the skin or tendons. They are a common and specific sign of congenital dyslipidaemia. Tendon xanthoma is specific to familial hypercholesterolaemia [20, 21], except for a few other rare conditions (cerebrotendinous xanthomatosis [22], type III hyperlipoproteinaemia [23], overproduction of apolipoprotein B [24] and betasitosterolaemia [25]). The presence of tendon xanthoma is heavily weighted in the DLCNS (6 points). The sole presence of xanthoma implies a probable diagnosis of familial hypercholesterolaemia. Moreover, detection of tendon xanthoma is important for risk prediction, as the presence of tendon xanthoma is independently associated with a higher risk of cardiovascular events and more severe coronary artery disease [26–29]. The Achilles tendon is the most common site of tendon xanthomas [30, 31]. Achilles tendon xanthoma (ATX) is clinically characterised by nodules found in the tendons and traditionally sought during close clinical examination, which consists of inspection and palpation of the Achilles tendon. Clinical examination is subjective, depends strongly on the clinician's experience and is not sensitive; it is easy to miss early xanthoma. Imaging techniques like ultrasonography, computed tomography and magnetic resonance imaging have been used to improve ATX detection [32, 33]. Of these imaging methods, ultrasonography is the cheapest, fastest, most widely available and emits no radiation. The aim of the study was to determine whether ultrasound detects more ATX than clinical examination.

Patients and methods

Study design, setting and study population

Our study was a single centre cross-sectional study conducted from July 2019 to March 2020. Consecutive participants were included from the ambulatory lipid clinic at the Department of General Internal Medicine of the University Hospital of Bern. The eligibility criteria were age ≥18 years and an LDL-C value ≥4.0 mmol/l (ever measured without lipid-lowering treatment or, if on lipid-lowering treatment, estimated using the Australian Atherosclerosis Society's calculator) [34], as this yields 1 point on the DLCNS and since the present study planned to also include younger participants from a specialised lipid clinic. Previous studies found that the younger population with heterozygous familial hypercholesterolaemia may have lower LDL values and still have familial hypercholesterolaemia [19, 35]. Moreover, heterozygous familial hypercholesterolaemia may also be associated with a mild familial hypercholesterolaemia phenotype either due to strict adherence to a low-fat diet or genetics. The diagnosis of this mild phenotype is challenging, and the phenotype may manifest later in life [36]. Reasons for participant exclusion were Achilles tendon surgery or trauma and pregnancy (because of the prone position for the ultrasound examination and unreliability of cholesterol measurements during pregnancy). The ethics committee of the canton of Bern approved the study protocol and other study documentation (BASEC ID: 2019-00404). The ethics committee received information about protocol amendments and study end, as per local requirements. Written informed consent was signed by all participants. The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines.

Patient history and clinical examination

The baseline data of participants (medications, cardiovascular risk factors, comorbidities, lipid values without therapy, duration of lipid-lowering therapy) was collected from the medical history, available at the medical polyclinic of the University Hospital of Bern and from primary care practices. A detailed patient history including pain history, physical activity (via a physical activity questionnaire [37]) and diet (via a Mediterranean diet questionnaire [38]) was obtained from participants on the day of their clinical visit.

Patients had one clinical visit in the study, which was on the day of their consultation in the lipid clinic. The attending physicians from the ambulatory lipid clinic evaluated each patient as usual, by clinical examination, which included a search for tendon xanthomas and corneal arcus. Physicians were trained in the clinical assessment of Achilles tendon xanthoma by an expert in lipidology (NR) with 23 years' experience in diagnosing familial hypercholesterolaemia. One or more nodules found on palpation of the Achilles tendon were considered positive findings [39]. The sonographic examination of Achilles tendons was conducted prior to the consultation by an assessor blind to the clinical examination findings and other clinical information.

In order to reduce bias, the results of the Achilles tendon examination with ultrasound were neither transmitted to the patient nor to the attending physician. Likewise, to maintain the blind, the Achilles tendon examiner was not informed about the patient's clinical data or the results of the clinical examination of the Achilles tendon. All ultrasound images were second-read by a rheumatologist with expertise in musculoskeletal ultrasound who was also blind to the patient's clinical data and the results of the clinical and sonographic examination.

Ultrasonographic examination

In all patients, the ultrasound examinations were performed by an internal medicine resident who had been trained in Achilles tendon sonography by a specialist with expertise in musculoskeletal ultrasound (BM). Philips equipment (Affiniti 50G, release 2.0.1) with a high-frequency linear probe (12–3 MHz) was used. As suggested in previous studies [40–42], Achilles tendons were examined in patients lying prone, with ankles extended beyond the examination bed and feet at 90° flexion (active positioning). Focal hypoechogenic nodule(s) within the tendon or diffuse hypoechogenicity with heterogeneous echostructure (echogenicity grade 1 or echogenicity grade 2, respectively) were considered to represent ATX (figure 1), provided that the patient had no history of trauma or surgery [33, 43–45]. Focal hypoechoic lesions (grade 1) were hypothesised to represent small clusters of macrophage-like

cells filled with esterified cholesterol. More extensive lipid accumulation in the Achilles tendon associated with a granulomatous reaction, inflammation, oedema and tendon fibre disorganisation and degeneration could explain the sonographic grade 2 anomalies [43]. Since ATX are usually accompanied by an increase in tendon size (caused by the accumulation of intratendinous lipids, as well as oedema and inflammation of the area) [30], ATX can also be diagnosed by measuring Achilles tendon thickness (AT-T) [40–42]. Measurements of AT-T were made in transverse and sagittal scans at the point of maximum thickness of the Achilles tendon. In uniformly sized tendons, measurements were taken 2 cm proximally to insertion in the os calcis. The mean AT-T from right and left AT-Ts were calculated from both transverse and sagittal scans. The sonography of both Achilles tendons in the present study took about 5–10 minutes.

Diagnostic criteria for ATX

For the sonographic detection of the ATX, several definitions and cut-off values of AT-T exist (appendix table S1). For the main analysis in this study, we used a definition given by the study of Junyent et al. [40], as it was the largest, most recent European study: abnormal echostructure of the right or left Achilles tendon (hypoechoic nodules or diffuse hypoechogenicity with heterogeneous echostructure) and/or mean AT-T above age- and sex-adjusted cut-off (5.3 and 5.7 mm in men ≤ and >45 years; 4.8 and 4.9 mm in women ≤ and >50 years, respectively). As sensitivity analyses, we used the ATX definitions suggested by Descamps et al. [41], Michikura et al. [42] and Scheel et al. [46] (appendix table S1).

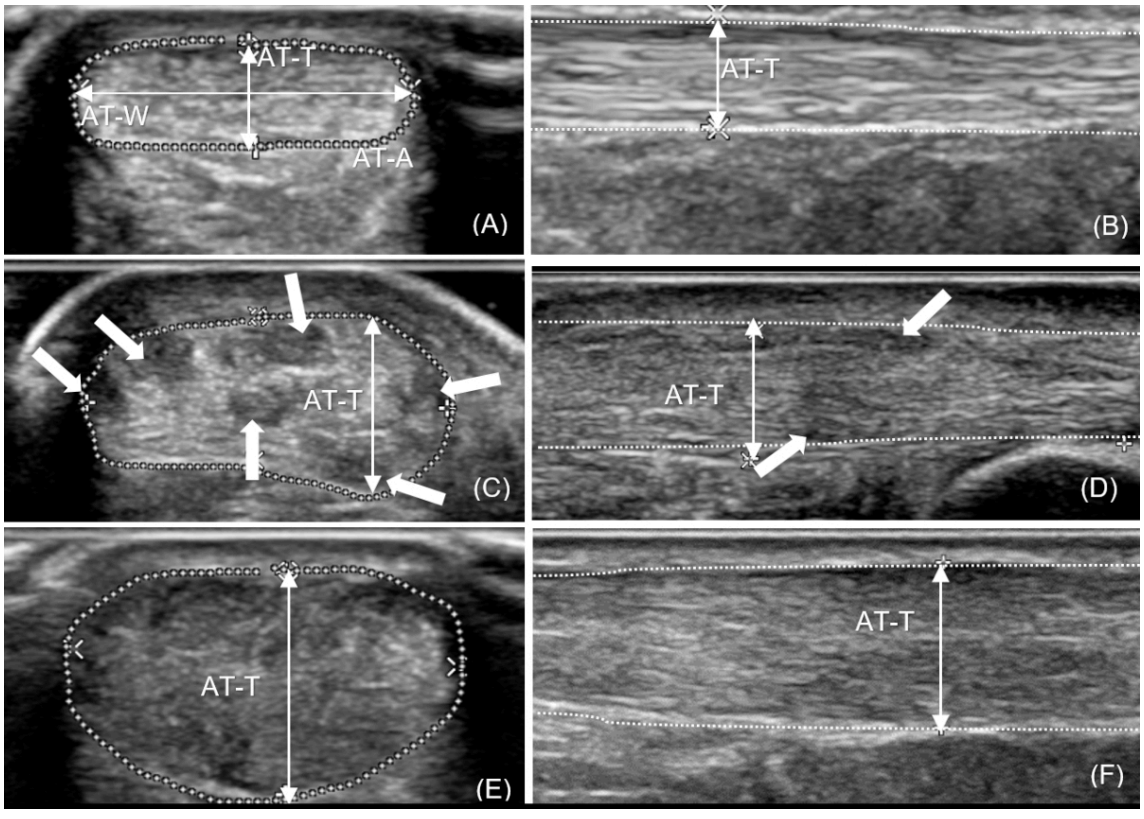
Primary and secondary endpoints

The primary endpoint was the ultrasonographic visualisation of the ATX. We compared the proportion of patients with ATX detected by either clinical examination or ultrasound. The secondary endpoint was reclassification of patients on the DLCNS after the ultrasound evaluation. The attending physicians from the ambulatory lipid clinic assessed each patient, by clinical examination, and calculated the DLCNS. The DLCNS was calculated again after ultrasound examination, and we compared the proportion of patients with probable/definite familial hypercholesterolaemia before and after ultrasound. Patients with a DLCNS ≥6 were classified as probable/definite familial hypercholesterolaemia, as recommended [47].

Statistical analysis

Descriptive results (baseline data) are expressed as number of participants (percentage) or as mean±SD. Mean values of AT-T, Achilles tendon width (AT-W) and Achilles tendon area (AT-A) were shown separately for men and women as well as for all study participants and for participants with ATX detected by ultrasound. A diagnosis of familial hypercholesterolaemia was considered "definite" if the total DLCNS was greater than 8, "probable" if it was 6–8, "possible" if 3–5 and "unlikely" if the score was

Figure 1: Visualisation of Achilles tendon on ultrasound. (**A**), (**C**), (**E**) transverse scans of the Achilles tendon; (**B**), (**D**), (**F**) sagittal scans. (**A**)–(**B**) normal thickness and echogenicity with fibrillary structure; (**C**)–(**D**) xanthomas (echogenicity grade 1): focal hypoechogenic areas (nodules) within the tendon (thick white arrows); (**E**)–(**F**) xanthomas (echogenicity grade 2): diffuse hypo- and heteroechogenicity with lost fibrillary structure. AT-T, Achilles tendon thickness (thin vertical arrows). AT-W, Achilles tendon width (thin horizontal arrow). AT-A, Achilles tendon area.



under 3. Patients with values of DLCNS ≥6 were classified as "probable/definite" familial hypercholesterolaemia. [47]. The reclassification rate was defined as the percentage of patients whose DLCNS score increased from <6 ("unlikely/possible") to ≥6 ("probable/definite") after the ultrasound examination.

To assess agreement between the ultrasound examiner and the second reader for the interpretation of Achilles tendon echogenicity on ultrasound, a kappa test was performed. The kappa coefficient for agreement between the examiner and the second reader was 0.681.

The power calculation was based on the results of previous studies [40, 45, 48]. Assuming a xanthoma detection rate of 20% in the clinical examination and a xanthoma detection rate of 40% in the ultrasound examination, 98% power to detect such rates with 100 participants was expected.

All analyses were performed using Stata Statistical Software (Stata 16; StataCorp).

Results

Of 213 people screened, 172 were eligible and 100 were included in the study (figure 2).

Mean (SD) age was 47 (12) years, mean (SD) peak LDL-C was 6.57 (2.2) mmol/l and mean (SD) lipoprotein a, or Lp(a), was 57.2 (78.7) nmol/l. Only 9/100 Lp(a) values were missing; 27/91 (24.6%) patients had elevated Lp(a) (>75 nmol/l). 49% of participants were women, 91% had no history of atherosclerotic cardiovascular disease (table 1), 43% had at least one first-degree relative with known premature (<55 years for men; <60 years for women) cardiovascular disease, 56% were currently receiving or had in the past received lipid-lowering therapy, for a mean duration of 4.03 years. ATX was detected by clinical examination in 23% of participants and by ultrasound in 60%. The mean (SD) AT-T in women with xanthoma diagnosed by ultrasound was 5.91 (1.79) mm and in men was 6.50 (1.53) mm (table 2). The mean (SD) peak LDL-C in the group with sonographically detected ATX was lower than that of participants with clinically detected ATX (6.80 [2.00] vs 7.94 [2.14]), but higher than that of subjects without ATX (6.18 [2.55]). The mean Lp(a) (SD) in the group with sonographically detected ATX was slightly higher than that of participants with clinically detected ATX and than that of subjects without ATX (61.2 [10.4] nmol/l vs 52.2 [11.9] nmol/l vs 50.7 [14.8] nmol/l).

Concordance between clinical and sonographic examinations

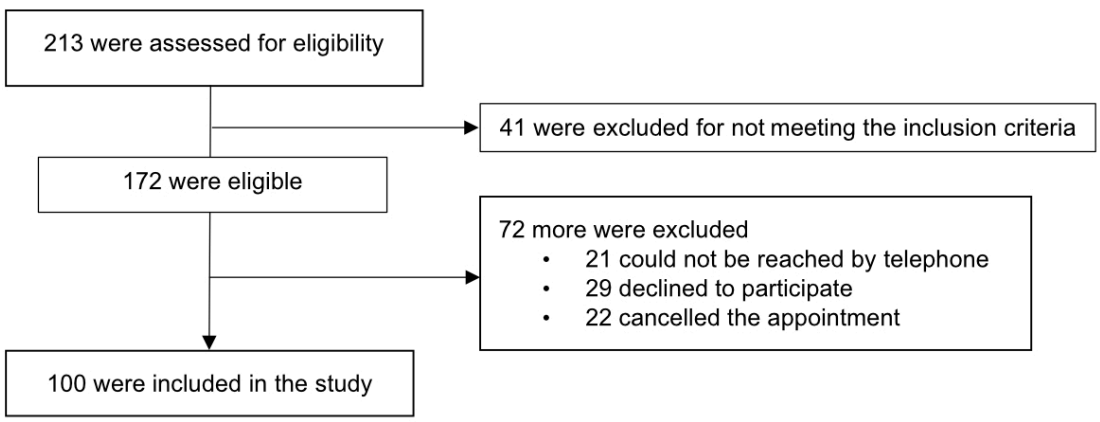
After the ultrasound examination, the diagnostic certainty of familial hypercholesterolaemia according to the DLCNS changed from "unlikely/possible" to "probable/definite" (cut-off at 6 points on the DLCNS) in 32% of participants (table 3). 43% of participants were in the "probable/definite" category after clinical examination (11% probable, 32% definite) and 72% after ultrasonography (14% probable, 58% definite). With the cut-off at 9 points (definite diagnosis), the performance of the DLCNS increased from 32% to 58%. 3% were reclassified from "probable/definite" to "unlikely/possible" after the ultrasound imaging. In these 3 patients, ATX was suspected on clinical examination (by the attending physician), whereas the Achilles tendon appeared normal in ultrasonography and AT-T was below the cut-off according to all definitions.

In sensitivity analyses using other criteria, the sonographic detection rate of ATX varied from 33% to 53% and the percentage of reclassification from "unlikely/possible" to "probable/definite" in DLCNS ranged from 13% to 25% (appendix table S2).

Echogenicity

51% of participants were classified as having at least one Achilles tendon with abnormal echogenicity (46% in the right, 42% in the left, 37% in both tendons). Echogenicity grade 1 (focal hypoechogenic area(s)/nodule(s) within the tendon) was seen in 42% of participants (38% of right and 33% of left tendons) and echogenicity grade 2 (diffuse hypo- and heteroechogenicity with lost fibrillary structure) in 10% of participants (8% of right and 9% of left tendons). Considering only the echogenicity criteria, 24% of participants were reclassified from "unlikely/possible" to "probable/definite" on the DLCNS. In 12% of participants, the echogenicity was interpreted as abnormal (11 with echogenicity grade 1 and 1 with echogenicity grade 2), but the Achilles tendon thickness was normal (under the AT-

Figure 2: Study flow diagram.



T cut-off of Junyent et al.) [40]. 48% of participants had a mean AT-T above the cut-off. Considering only the thickness criteria, 26% of participants were reclassified from "unlikely/possible" to "probable/definite" on the DLCNS.

Table 1:
Baseline characteristics of participants.

		100 participants
Characteristics		
Age – years, mean (SD)[range]		47.3 (12.3) [19–77]
Women, %		49
History of cardiovascular disease, %		9
	Premature cardiovascular disease, %	8
	Coronary, %	6
	Cerebral or peripheral, %	2
Family history of premature cardiovascular disease*, %		55
Hypertension, %		29
Diabetes mellitus, %		2
Current smoker, %		14
Previous smoker, %		34
Mean body mass index, kg/m^2 (SD) [range]		26.14 (4.28) [16.97–36.64]
Lipid-lowering therapy, current or past, %		56
Mean duration of lipid-lowering therapy, years, mean (SD) [range]		4.03 (4.7) [0.1–23]
Pain in left or right Achilles tendon, current or past, %		14
	Currently, %	3
Laboratory results, mean (standard deviation) [range]		
Peak (untreated) LDL cholesterol, mmol/l**		6.57 (2.20) [4.03–19.52]
On the day of examination	Total cholesterol, mmol/l	6.20 (1.70) [2.90–10.97]
	LDL cholesterol, mmol/l	4.02 (1.45) [1.05–8.57]
	HDL cholesterol, mmol/l	1.43 (0.39) [0.61–2.60]
	Triglycerides, mmol/l	1.82 (1.47) [0.49–8.88]
	Lipoprotein(a), nmol/l***	57.19 (78.73) [7–441]

* First-degree relative with known premature (<55 years, men; <60 years, women) cardiovascular disease.

** 94% measured without lipid-lowering therapy, 6% with lipid-lowering therapy (in whom Australian Atherosclerosis Society calculator used [34])

*** 9/100 lipoprotein(a) values were missing; 27/91 (24.6%) patients had elevated lipoprotein(a) (>75 nmol/l).

Table 2:
Sonographic measurements of Achilles tendon thickness, width and area in all study subjects and in those diagnosed with xanthoma by ultrasound.

Values are presented as mean (standard deviation) [range].

	All study subjects	**Subjects diagnosed with xanthoma by ultrasound**	**Subjects diagnosed without xanthoma by ultrasound**
AT-T, mm			
Women	5.28 (1.58) [3.79–12.85]	5.91 (1.79) [3.79–12.85]	4.36 (0.26) [3.95–4.81]
Men	5.83 (1.48) [3.94–11.93]	6.50 (1.53) [4.4–11.93]	4.81 (0.45) [3.94–5.67]
AT-W, mm			
Women	13.06 (2.15) [8.76–23.4]	13.43 (2.53) [10.35–23.4]	12.51 (1.30) [8.76–15.2]
Men	14.48 (2.23) [11.05–20.4]	15.00 (2.28) [11.80–20.40]	13.66 (1.94) [11.05–18.25]
AT-A, cm^2			
Women	62.47 (36.33) [30.6–288]	71.28 (45.06) [45.70–288]	49.7 (7.24) [30.6–65.25]
Men	71.61 (23.60) [29.29–152.5]	80.24 (24.98) [39.05–152.5]	58.24 (13.06) [29.29–74.5]

AT-T: Achilles tendon thickness; AT-W: Achilles tendon width; AT-A: Achilles tendon area.

Table 3:
Detection rate of Achilles tendon xanthomas and rate of people classified in the "probable" or "definite" category on the DLCNS after clinical examination and after ultrasound and reclassification rate on DLCNS after ultrasound.

	Detection rate of ATX	**"Probable/definite" category on the DLCNS**	**Reclassification rate from "unlikely/possible" to "probable/definite" on DLCNS after ultrasound**
Clinical examination	23%	43%	N.A.
Ultrasound examination according to definition of Junyent et al. [40]*	60%	72%**	32%***

ATX: Achilles tendon xanthoma; DLCNS: Dutch Lipid Clinic Network Score; AT-T: Achilles tendon thickness, N.A.: not applicable.

* AT-T >5.3 and >5.7 mm in men ≤ and > 45 years, AT-T >4.8 and >4.9 mm in women ≤ and >50 years AND/OR abnormal echogenicity: hypoechogenic nodule(s) within the tendon and/or diffuse hypo- and heteroechogenicity with lost fibrillary structure.

** DLCNS calculated after clinical and ultrasound examination.

***3 patients were reclassified from "probable/definite" to "unlikely/possible" after the ultrasound examination (according to all definitions), which explains why the reclassification rate is not equal to the difference between the rate of people in the "probable/definite" category on the DLCNS after ultrasound and after clinical examination: 72–(43–3) = 32.

Nine patients were diagnosed with xanthoma based only on the thickness criteria and the Achilles tendon had a normal echogenicity (8/9 of these patients were reclassified from "unlikely/possible" to "probable/definite" on the DLCNS).

Discussion

In this cross-sectional study of 100 patients from a tertiary centre ambulatory lipid clinic, using ultrasound of the Achilles tendon more than doubled the detection of ATX compared to clinical examination, but the detection rate depended strongly on the definition of ATX on ultrasound. The more sensitive detection of ATX by ultrasound translated into an increased reclassification rate from "unlikely/possible" to "probable/definite" on the DLCNS, namely from 43% to 72%.

Our study explored different sonographic ATX definitions, and according to all of them, the detection rate of ATX as well as the reclassification rate increased to a clinically meaningful extent. Our findings regarding sonographic detection of ATX are comparable to other studies. Junyent et al. [40] detected ATX in 43% by clinical examination and in 68% by ultrasonography. Jarauta et al. [48] showed an ATX detection rate of 27.6% and 56.6%, whereas Ebeling et al. [45] reported 43% and 77%, respectively.

Since different sonographic criteria for ATX exist, it remains uncertain which ones should be used and whether or not echogenicity should be taken into account. This uncertainty is reflected in the latest systematic review of diagnostic accuracy of ultrasound for ATX in people with familial hypercholesterolaemia [49], in which the authors pointed out the lack of consistent diagnostic criteria. Most ultrasound-diagnosed ATX cases in our study had both a thickening and echogenicity changes. However, nine of our patients diagnosed with ATX by ultrasonography (eight of them were reclassified on the DLCNS) had a uniformly thickened Achilles tendon with normal echogenicity. The direct impact of hypercholesterolaemia on tendons involves cholesterol deposits within tendon tissues, along with changes in the tendon's mechanical properties [50–53]. From a pathophysiological viewpoint, it seems therefore inconsistent to diagnose xanthoma without changes in tendon echogenicity. Future studies to assign clear diagnostic criteria are needed. Future studies using genetics as the gold standard should further evaluate the increases in sensitivity and specificity achieved with different cut-offs for AT-T and whether the echogenicity criterion (hypoechogenic nodule(s) within the tendon or diffuse hypo- and heteroechogenicity with lost fibrillary structure) also increases sensitivity and specificity. Interestingly, the mean Lp(a) in the group with sonographically detected ATX was slightly higher than that of participants with clinically detected ATX (mean 61.2 nmol/l [SD 10.4] vs 52.2 nmol/l [SD 11.9]). Elevated plasma Lp(a) levels are detectable in approximately 30–50% of patients with familial hypercholesterolaemia [54], and consistent findings suggest that they may significantly contribute to and independently predict risk of cardiovascular disease in these individuals. This value is used in the SAFEHEART Risk Equation, a stratification tool for the risk of cardiovascular disease in patients with familial hypercholesterolaemia [55]. Another open question is whether ultrasound is able to distinguish between xanthoma and other Achilles tendinopathies like overuse tendinopathy associated mainly with advanced age and obesity, tendinopathy caused by sports, diabetes, rheumatoid arthritis, fluoroquinolones or glucocorticoid use [56]. Many of these entities can be excluded through a careful assessment of the medical history, and examination of a selected population should minimise the likelihood of confusing xanthoma with other tendinopathies. It is possible that more sophisticated measurement techniques in the hands of musculoskeletal ultrasonography specialists, e.g. quantification of the tendon area in horizontal planes or pathological blood vessel formation as indicated by power Doppler ultrasound, might further improve the diagnostic accuracy of xanthoma diagnosis by ultrasound imaging.

A further question that may arise concerns the cost-effectiveness of this additional ultrasound examination. Although duration was not formally recorded in our study, it took about 5–10 minutes per patient to perform the ultrasound of the Achilles tendons. The time and economic burden of this extra examination seems low. However, it was not the aim of our study to perform a cost-effectiveness analysis. Future studies should evaluate this question.

Limitations

Genetic testing is considered the "gold standard" for diagnosing familial hypercholesterolaemia, but although this aspect was considered during study design and buffy coats for genetic analyses were collected in all but 5 patients, the genetic analyses were finally not available in the current study due to lack of funding. However, the sonographic criteria used in the current study were derived from large European studies with genetically confirmed familial hypercholesterolaemia [40, 41] and several sensitivity analyses were performed using different cut-offs. Moreover, even with a negative genetic test, there is still a risk of having familial hypercholesterolaemia with a hitherto undiscovered genetic trait (~20–40% missed "definite" familial hypercholesterolaemia) [57, 58]. Nevertheless, due to the lack of a gold standard, we might have misclassified our familial hypercholesterolaemia diagnoses, mainly among patients without xanthoma, as xanthoma is very specific for familial hypercholesterolaemia (specificity of earlier studies using ultrasound xanthoma in genetically confirmed patients: 78–100%, see appendix table S1) [40–42, 45, 46, 59]. However, since different sonographic criteria for ATX exist, future studies to establish clear, standardised and uniform diagnostic criteria are needed. Second, the DLCNS was not developed/validated for ATX diagnosed by ultrasound, but only for diagnosis by clinical examination. We therefore cannot definitively conclude that the increased reclassification rate on the DLCNS translated into more correct diagnoses of familial hypercholesterolaemia. Nevertheless, xanthoma is highly specific for familial hypercholesterolaemia [40–42, 45, 46, 59] and the DLCNS could be limited by the imprecise diagnosis of ATX solely by clinical examination and more studies are needed to study the added value of ATX diagnosis by ultrasound in DLCNS. Third, our population was a selected population from a lipid clinic, with a higher likelihood of a diagnosis of familial hypercholesterolaemia, so the results cannot be directly applied to the general pop-

ulation. Fourth, ultrasound imaging depends on the technical skills of the investigator. To alleviate this limitation, we used a very simple semi-quantitative brightness-mode evaluation, and measured the maximal sagittal diameter of the tendon at its thickest location in sagittal and horizontal planes, thereby ensuring that this examination is easy to be applied.

Clinical implications

Earlier studies have shown that the diagnosis of xanthoma can help better identify familial hypercholesterolaemia patients and has some prognostic information: at any level of LDL-C, the prognosis for patients with familial hypercholesterolaemia and xanthoma is much worse than for those with familial hypercholesterolaemia but without xanthoma [7, 28]. According to a recent study [60], the prevalence of ATX only detected by ultrasound was higher in genetically positive than negative familial hypercholesterolaemia patients. The ultrasound examination also showed a higher concordance with the genetic diagnosis than the clinical examination. This quick, inexpensive and easy-to-implement ultrasound examination could potentially help clinicians initiate additional evaluations and referral to specialised centres to detect familial hypercholesterolaemia in suspected patients, especially in settings where genetic tests are not easy to be performed or not reimbursed, such as in Switzerland. The usability of this examination in GP practices needs to be further evaluated in future studies. Moreover, 10% to 25% of statin users complain about side effects (or nocebo effect), most commonly muscle symptoms [61, 62]. Many patients stop taking statins, and cessation of the treatment is associated with worse cardiovascular outcomes and increased mortality [61, 62]. Therefore, additional certainty about the clinical diagnosis of familial hypercholesterolaemia may help to target treatment to the high-risk patients and to convince patients that this treatment is necessary to reduce their cardiovascular risk.

Conclusion

Compared to clinical examination, ultrasound of Achilles tendon substantially increases the detection of ATX and has shown high specificity in earlier studies. Future studies should evaluate whether the addition of ultrasound of the Achilles tendon contributes to earlier diagnosis of familial hypercholesterolaemia in patients who are at high risk for premature cardiovascular disease, e.g. via increased rate of referral for genetic testing.

Author contributions

The authors confirm contribution to the paper as follows: study conception and design: MDM, NR, MF, EM; data collection: MDM, DP, JA; analysis and interpretation of results: MDM, MF, MB, EM, NR, SB, BM, JA; writing and preparation of the manuscript: MDM, SB. All authors reviewed the results and approved the final version of the manuscript.

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Potential competing interests

All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. No potential conflict of interest related to the content of this manuscript was disclosed.

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Appendix

Table S1:
Different diagnostic criteria and AT-T cut-off values for the diagnosis of Achilles tendon xanthomas.

Author of the study	Year, country	FH group	Non-FH group	Diagnostic criteria/ AT-T cut-off	Sensitivity	Specificity
Ebeling et al. [45]	1992, Finland	30	58	AT-T>5.9mm	97%	83%
				AT-breadth >13 mm	87%	81%
				Hypoechogenic echostructure	89%	100%
				All 3 criteria above	93%	96%
Koivunen-Niemela et al. [60]	1993, Finland	40	92	AT-T>10mm in men, >9mm in women	63%	94%
				AND/OR		
				Hypoechogenic echostructure	90%	94%
Descamps et al. [41]	2001, Belgium	127	160	AT-T> 5.8 mm (no criterion of abnormal echogenicity)	75%	85%
Scheel et al. [46]	2004, Germany	22	21	AT-T> 6 mm AND/OR abnormal echogenicity: hypoechogenic nodule(s) within the tendon and/or diffuse hypo- and heteroechogenicity with lost fibrillary structure	91%	91%
Junyent et al. [40]	2005, Spain	127	221	AT-T >5.3 and >5.7mm	≤45 y: 49%	≤45 y: 91%
				in men ≤ and >45 years,	>45 y: 75%	>45 y: 89%
				And >4.8 and >4.9mm	≤50 y: 50%	≤50 y: 88%
				in women ≤ and >50 years	>50 y: 67%	>50 y: 81%
				AND/OR		
				abnormal echogenicity: hypoechogenic nodule(s) within the tendon and/or diffuse hypo- and heteroechogenicity with lost fibrillary structure	nr	100%
Michikura et al. [42]	2017, Japan	130	155	AT-T >5.8 mm in men, >5.5 mm in women (no criterion of abnormal echogenicity)	m: 71%	m: 78%
					w: 80%	w: 81%

nr, not reported; m, men; w, women

Table S2:
Detection rate of Achilles tendon xanthomas and rate of persons classified in the "probable" or "definite" category on the DLCNS after clinical examination and after US and reclassification rate on DLCNS after US according to different definitions.

		Detection rate of ATX	"Probable/definite" category on the DLCNS	Reclassification rate from "unlikely/possible" to "probable/definite" on DLCNS after US*
Clinical examination		23%	43%	N.A.
Ultrasound examination	Junyent et al. [40]	60%	72%**	32%
	Scheel et al. [46]	53%	65%**	25%
	Michikura et al. [42]	36%	55%**	15%
	Descamps et al. [41]	33%	53%**	13%
	Only echogenicity criteria***	51%	64%**	24%

ATX, Achilles tendon xanthoma; DLCNS, Dutch Lipid Clinic Network Score; US- Ultrasound; AT-T, Achilles tendon thickness

***** 3 patients were reclassified from "probable/definite" to "unlikely/possible" after the US examination (according to all definitions), that is why the reclassification rate is not equal the difference between the rate of persons in **"**probable/definite" category on the DLCNS after US and after clinical examination

** DLCNS calculated after clinical and ultrasound examination

*** focal hypoechogenic nodule(s) within the tendon or diffuse hypo- and heteroechogenic tendon with lost fibrillary structure