

Review

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Measurement of Achilles tendon thickness using ultrasonography for diagnosis and risk assessment in patients with familial hypercholesterolemia

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Abstract

Familial hypercholesterolemia (FH) is an autosomal dominant inherited disorder characterized by elevated low-density lipoprotein cholesterol (LDL-C) levels and skin and/or tendon xanthomas. FH is caused by mutations in genes associated with the LDL receptor pathway. Heterozygous FH is frequently encountered, occurring in about one in 300 people, one in 30 people with coronary artery disease, and one in 15 people with premature coronary artery disease or severe hyperlipidemia. Because FH patients are exposed to high LDL-C concentrations from birth, this leads to progressive atherosclerosis, and the development of cardiovascular events in these patients is 15-20 years younger than the typical age of onset. Achilles tendon thickening is the most specific physical finding in FH, although it is also observed in patients with metabolic diseases such as sitosterolemia and cerebral tendon xanthomatosis and in cases of Achilles tendon rupture. In Japan, FH criteria include Achilles tendon thickening as a diagnostic criterion in addition to the presence of tendon xanthomas. Furthermore, thicker Achilles tendons are associated with a higher risk of cardiovascular events. Therefore, the measurement of Achilles tendon thickness is beneficial not only for the diagnosis of FH but also for cardiovascular event risk assessment. It is hoped that the measurement of Achilles tendon thickness will improve diagnostic performance and lead to earlier diagnosis and reduced incidence of coronary artery disease. This review summarizes the usefulness of measuring Achilles tendon thickness for diagnosis and risk assessment of cardiovascular events in FH.

Keywords: Familial hypercholesterolemia, Achilles tendon, ultrasonography, radiography, risk assessment



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INTRODUCTION

Familial hypercholesterolemia (FH) is an inherited disorder that causes very high levels of low-density lipoprotein cholesterol (LDL-C). Heterozygous FH is frequently encountered, occurring in about one in 300 people, one in 30 people with coronary artery disease, and one in 15 people with premature coronary artery disease or severe hyperlipidemia^[1]. Because FH patients are exposed to high LDL-C concentrations from birth, this leads to progressive atherosclerosis, and the development of cardiovascular events in these patients is younger than the typical age of onset. Therefore, early diagnosis and treatment of FH are very important to improve prognosis. However, although FH is a relatively common hereditary disorder, its diagnostic rate remains low^[2]. Achilles tendon thickening is a specific physical finding in patients with FH. Thicker Achilles tendons are associated with a higher risk of cardiovascular events. Therefore, the measurement of Achilles tendon thickness is beneficial not only for the diagnosis of FH but also for cardiovascular event risk assessment.

However, Japan is the only country in the world where Achilles tendon thickness is included as a criterion for diagnosing FH. To improve the diagnostic rate of FH globally, it is essential to promote the widespread use of ultrasonography, which is a simple and accurate method for measuring Achilles tendon thickness.

In this review, we summarize the usefulness of measuring Achilles tendon thickness for diagnosis and risk assessment of cardiovascular events in FH.

FAMILIAL HYPERCHOLESTEROLEMIA?

What is familial hypercholesterolemia?

FH is an autosomal dominant inherited disorder characterized by elevated LDL-C levels, skin and/or tendon xanthomas, and early-onset coronary artery disease (CAD) due to premature atherosclerosis^[3,4]. FH is caused by mutations in genes associated with the LDL receptor pathway. The majority of causative genes are *LDLR* mutations, with proprotein convertase subtilisin/kexin type 9 (*PCSK9*) gain-of-function mutations accounting for approximately 5% of heterozygous FH (HeFH). Apolipoprotein B (*APOB*) mutations are relatively common in Europe but extremely rare in Japan^[5]. HeFH is frequently encountered, occurring in about one in 300 people, one in 30 people with coronary artery disease, and one in 15 people with premature coronary artery disease or severe hyperlipidemia^[1]. Homozygous FH (HoFH), on the other hand, is found in one or more people in 360,000 to 1 million of the population. Because FH patients are exposed to high LDL-C concentrations from birth, this leads to progressive atherosclerosis and the onset of cardiovascular events in these patients occurs 15-20 years earlier than the typical age of onset^[2]. Early diagnosis and appropriate treatment are necessary to prevent the development of CAD.

Xanthomas and Achilles tendon thickening

The diagnosis of FH is based on untreated LDL-C levels, family history, the presence of xanthomas, and genetic analysis. Xanthomas occur most frequently in areas subject to mechanical stress, such as the elbows, knees, wrists, and buttocks. Xanthomas are a characteristic physical finding of FH and a decisive factor in its diagnosis. The Dutch Lipid Clinic Network FH criteria^[6], Simon-Broome diagnostic criteria^[7], and Make Early Diagnosis to Prevent Early Death^[8] include tendon xanthomas in their FH diagnostic criteria. In 1977, Mabuchi reported that FH could be detected from Achilles tendon thickness using radiography^[9]. As a result, the Japan Arteriosclerosis Society (JAS) FH criteria included Achilles tendon thickening as a diagnostic criterion in addition to the presence of tendon xanthomas, defining Achilles tendon thickening as Achilles tendon thickness of 9 mm or more by soft radiography for both sexes^[10]. However, there were several problems with this definition. First, while the specificity for diagnosis was very high, sensitivity was low. The reason for this is thought to be that although gender differences in Achilles tendon thickness are

observed, no gender-specific cutoff values have been set, making women less likely to be diagnosed with FH. Second, this threshold was established when statins were not available. Finally, the threshold was not determined by statistical analysis using ROC curves. Therefore, based on the results of an analysis of 986 cases in Japan^[11], the 2022 edition of the JAS FH criteria set gender-specific reference values for Achilles tendon thickness by radiography at 8.0 mm for men and 7.5 mm for women, which improved diagnostic sensitivity while ensuring specificity.

On the other hand, approximately 30% of patients with FH do not exhibit Achilles tendon thickening^[12]. In general, xanthomas, if present before adulthood, tend to be mild, and they often become more pronounced with aging. However, there are also cases in which tendon xanthomas are absent even in elderly individuals. Possible reasons for the reduced tendency of Achilles tendon thickening include early therapeutic intervention and genetic factors related to FH^[13]. We analyzed the relationship between AT thickness and carotid intima-media thickness (IMT) in 450 patients clinically diagnosed with heterozygous FH. Among teenagers, no carotid IMT thickening was observed; however, 39% of the subjects exhibited AT thickening. These findings suggest that AT thickness is a more sensitive indicator than carotid IMT for assessing the degree of lipid deposition in tissues, particularly in young adults^[14].

Regression of Achilles tendon xanthoma in FH by lipid-lowering drugs and LDL-apheresis

Thickened Achilles tendon in patients with FH is composed of cholesterol, macrophage-derived foam cells, and other components. Therefore, it is expected that a reduction in LDL-C through pharmacological therapy would lead to the removal of lipid components, resulting in a decrease in Achilles tendon thickness. However, reports of actual tendon regression following pharmacological treatment are relatively rare.

Probucol has been reported to have a certain degree of LDL-C lowering effect even in homozygous FH and has been associated with the reduction or disappearance of xanthomas in the skin and Achilles tendon^[15]. Statins, which are frequently used in FH, have also been reported to reduce Achilles tendon thickness^[16]. However, in this report, regression was observed in normal, non-thickened Achilles tendons, whereas no significant change was observed in the group with thickened tendons.

In contrast, treatments that significantly lower LDL-C, such as PCSK9 inhibitors and apheresis, have been reported to result in a significant regression of the Achilles tendon over approximately three years^[17]. However, some studies have indicated that while PCSK9 inhibitors reduced carotid intima-media thickness (C-IMT), they had no effect on Achilles tendon thickness^[18]. The effects of ezetimibe, resins, microsomal triglyceride transfer protein (MTP) inhibitors and Angiopoietin-like 3 (ANGPTL3) inhibitors on the Achilles tendon remain unclear.

As these reports suggest, the relationship between lipid-lowering drugs and Achilles tendon regression has not been definitively established. Since Achilles tendon thickness reflects the cumulative burden of LDL-C, we believe that even if LDL-C is reduced, its long-term accumulation may prevent a significant regression of the tendon. In cases where Achilles tendon regression has been observed, we speculate that this may not be due to LDL-C reduction itself but rather to the improvement of inflammation-induced edema, potentially as a result of the antioxidant and anti-inflammatory effects of the treatment^[19].

MEASURING ACHILLES TENDON THICKNESS

Ultrasonography is affected by the presence of air or bone. However, since the Achilles tendon is located just beneath the skin, it can be clearly visualized without being affected by these factors, making it an accessible and effective imaging modality for anyone. Therefore, ultrasonography is a useful diagnostic tool

for tendon disorders^[20]. We have been working on establishing a method for the measurement of Achilles tendon thickness in patients with FH by ultrasonography since 2013. We analyzed 130 FH patients with genetic mutations and 155 non-FH patients. The Achilles tendon thickness in FH patients was 9.2 mm (5.8-11.7 mm) in men and 6.2 mm (5.6-9.7 mm) in women. Using ROC curves, the cutoff values for distinguishing FH patients were 6.0 mm in men (sensitivity: 63%, specificity: 85%) and 5.5 mm in women (sensitivity: 80%, specificity: 81%)^[21-23]. Based on this result, we reported Japan's first gender-specific thresholds for diagnosis by ultrasonography of 6.0 mm for men and 5.5 mm for women in 2017^[21]. A working group of the Japanese Society of Arteriosclerosis and the Japan Society of Ultrasonics in Medicine reported a standard method for measuring Achilles tendon thickness in 2018. Subsequently, these thresholds for Achilles tendon thickness by ultrasonography for FH diagnosis were adopted in the 2022 JAS FH criteria^[3]. Several reports have been published on the cutoff values of Achilles tendon thickness measured by ultrasonography for the diagnosis of FH in populations outside Japan. In Belgium, the cutoff value is 5.8 mm, with a sensitivity of 75% and a specificity of 85%^[24]. In Spain, the values differ by age and sex: for men aged 45 years or younger, the cutoff is 5.3 mm (sensitivity 49%, specificity 91%), and for those aged 46 years or older, it is 5.7 mm (sensitivity 75%, specificity 89%). For women aged 50 years or younger, the cutoff is 4.8 mm (sensitivity 50%, specificity 88%), and for those aged 51 years or older, it is 4.9 mm (sensitivity 67%, specificity 81%)^[25]. In the United States, the reported cutoff is 6 mm, with a sensitivity and specificity of 91%^[26]. Despite slight variations, there is no significant difference in cutoff values among these countries. Further research and the accumulation of data are necessary to facilitate a systematic review of this topic.

Cholesterol is used to repair Achilles tendons damaged due to weight-bearing or mechanical stimuli, but in FH, LDL-C is markedly elevated during growth when the frequency of injury and repair is high, and excess LDL is trapped in the extracellular matrix of the Achilles tendon. The LDL is then oxidatively denatured and phagocytosed by invading macrophages to form foam cells, which are deposited in the Achilles tendon, resulting in its thickening^[27] [Figure 1]. It is of note that smoking affected Achilles tendon thickening in our study^[21]. Tendon xanthomas are formed by focal infiltration of lipid-accumulating foamy macrophages into tendon cells, extracellular ester and non-esterified cholesterol deposits, and connective tissue^[28]. There is a positive correlation between the size of Achilles tendon xanthomas and autoantibody titers against oxidized LDL^[29]. Several pathways promote the formation of oxidized LDL, including inflammatory cytokines, increased oxidative stress, and macrophage activation^[30]. Smoking contributes to an increase in inflammatory cytokines, promotes LDL oxidation, and enhances its metabolism by macrophages^[31-35]. Therefore, smoking-induced inflammation and oxidative stress may increase phagocytosis of LDL trapped in the extracellular matrix by macrophages, thereby promoting oxidative degeneration^[36].

Additionally, the presence of Achilles tendon xanthomas in patients with FH has been reported to be associated with genetic mutations in the LDL oxidative pathway^[37], and the formation of Achilles tendon xanthoma is also linked to increased intracellular lipid content and a strong inflammatory response of macrophages to oxidized LDL^[38]. This suggests that the oxidative and inflammatory properties of LDL play an important role in the formation of Achilles tendon xanthomas. Furthermore, although the ultrasonographic and radiographic methods were well correlated in our study ($R = 0.924$, $P < 0.001$), the Achilles tendon was found to be thicker by radiography than ultrasonography^[21]. This may be due to the fact that in radiography, voltage and other parameters are adjusted to increase contrast, but the boundary between the Achilles tendon and skin is often unclear due to the similar degree of X-ray transmission for both of them [Figure 2]. Thus, skin and subcutaneous tissue may also be included in the Achilles tendon thickness measured. In addition, there is twisting in the Achilles tendon from the soleus and gastrocnemius muscles to the calcaneus^[39], and it is located at an angle to the direction of the X-ray beam. For this reason,

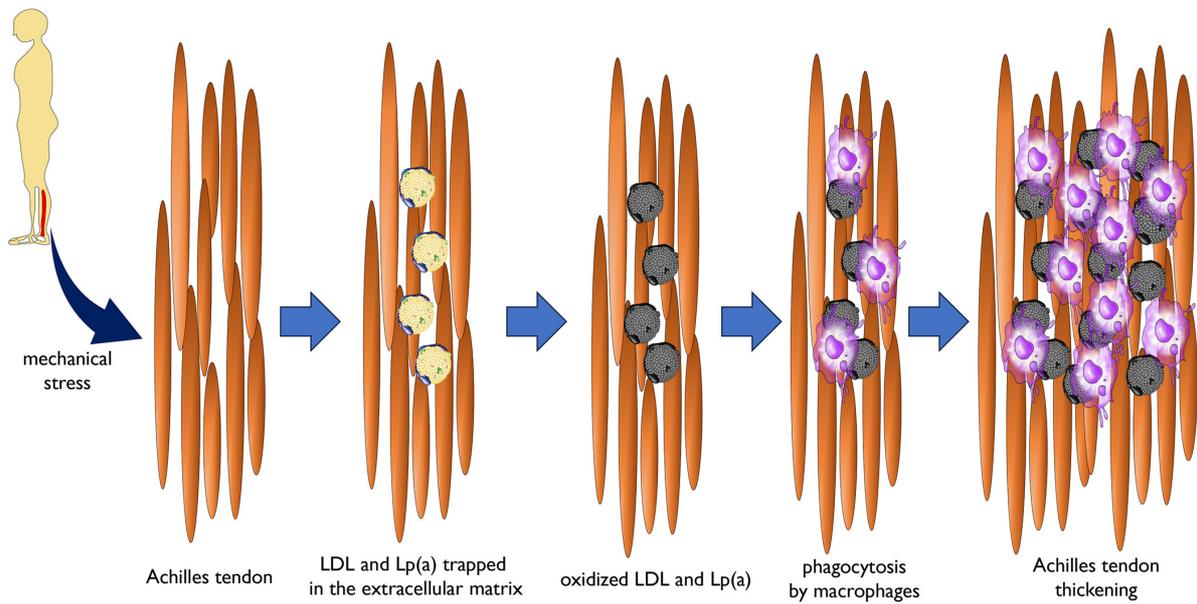


Figure 1. Mechanism of Achilles tendon thickening in patients with Familial hypercholesterolemia.

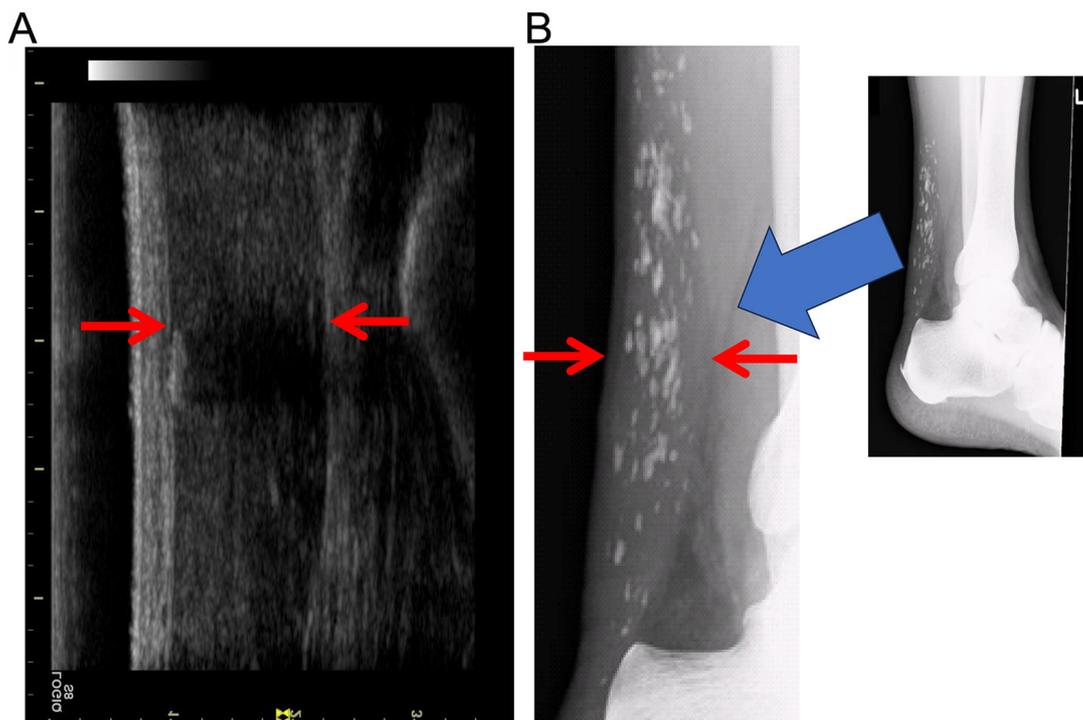


Figure 2. Achilles tendon image of a 77-year-old patient with Familial hypercholesterolemia by ultrasonography (A) and X-ray (B). The boundary of the Achilles tendon is clearly delineated by ultrasonography (A), but the boundary by X-ray is unclear (B).

radiographic methods that measure shading overestimate Achilles tendon thickness by the degree of torsion [Figure 3].

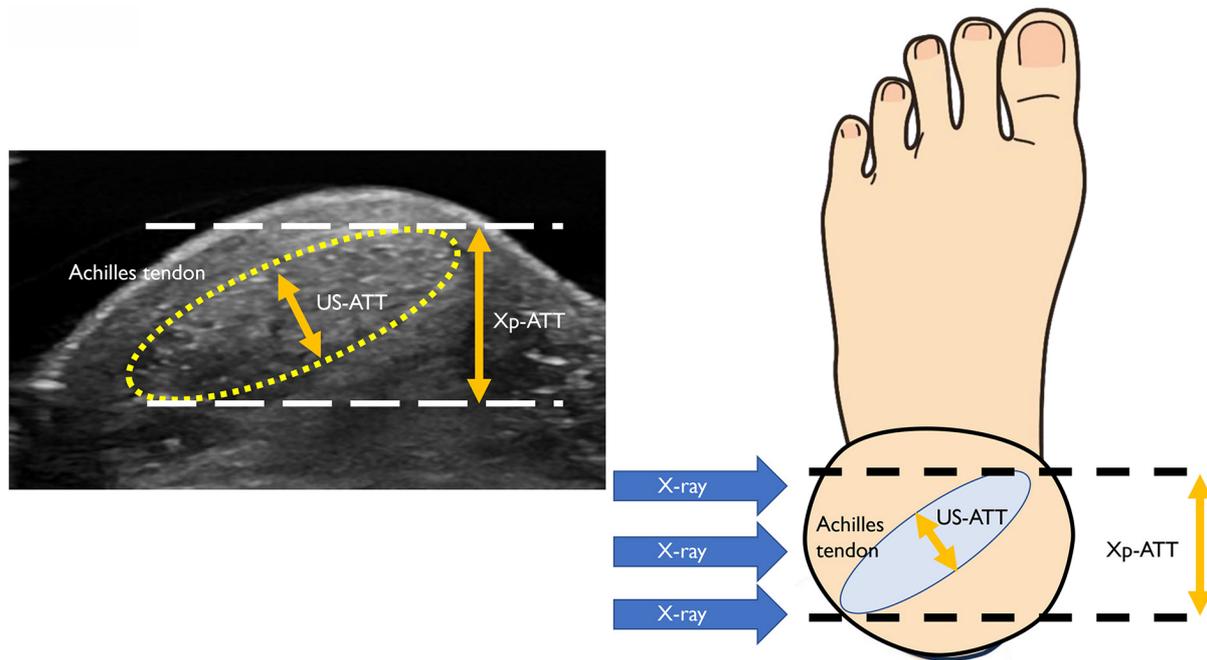


Figure 3. The problem of twisting in the Achilles tendon due to its orientation at an angle to the direction of the X-ray beam. US-ATT: Achilles tendon thickness measured by ultrasonography, Xp-ATT: Achilles tendon thickness measured by radiography.

In addition to ultrasound and X-ray methods, CT and MRI are also available modalities for evaluating the Achilles tendon. Bude *et al.* reported that ultrasound is superior to MRI in terms of contrast resolution and the ability to detect focal lipid deposits, making it the optimal method for detecting xanthomas^[40]. Similarly, Liem *et al.* also reported that MRI does not necessarily have a higher ability than ultrasound to distinguish FH^[41]. Moreover, a very strong correlation ($r = 0.96$) was observed between CT and ultrasound. While CT and MRI excel in the detailed assessment of tissue structures, they come with challenges such as high costs, longer imaging times, and radiation exposure, making ultrasound the preferred first-choice modality for Achilles tendon evaluation. Regarding MRI, there is potential for a novel evaluation method based on internal composition that utilizes differences in signal intensity between FH and non-FH cases^[42].

When measuring Achilles tendon thickness using the ultrasonic method, it is not necessary to prepare a dedicated device, as a general-purpose device can be used. The equipment utilized is a general-purpose ultrasound machine commonly used for examining the carotid artery and abdominal regions, with a high-frequency probe designed for imaging the carotid artery and superficial organs such as the thyroid gland and mammary glands. Therefore, this measurement can be performed in a wide range of medical institutions, including hospitals and clinics.

ASSOCIATION BETWEEN ACHILLES TENDON THICKNESS AND CARDIOVASCULAR EVENTS

The major complications of atherosclerosis in patients with FH include coronary artery disease, peripheral artery disease, and carotid atherosclerosis, while the mortality rate from stroke is not significantly different from that of the general population^[43]. Cardiovascular events begin to increase in FH from the age of 40 years in men and from the age of 50 years in women^[44], with a higher risk of developing coronary artery disease compared to non-FH^[6,45], and a five- to ten-fold higher odds ratio for peripheral artery disease compared to non-FH^[46]. Achilles tendon thickness is thought to reflect cumulative LDL-C levels, with

thicker Achilles tendons associated with a higher risk of cardiovascular events^[21-23]. In our study^[47], Achilles tendon thickening was observed in 95% of patients in the major adverse cardiac events (MACE) group and 63% in the non-MACE group. During a follow-up period of 1,239 days (700-1,827 days), Achilles tendon thickening increased the odds of cardiovascular events by 6.7 times (odds ratio [OR]: 6.67, 95% confidence interval [CI]: 2.39-18.63, $P < 0.001$), while tendon softening increased the odds by 4.9 times (OR: 4.93, 95%CI: 1.86-13.08, $P < 0.001$). Additionally, Tada *et al.* reported^[21-23] that in the group with Achilles tendon thickening, the hazard ratios were 2.73 (95%CI: 1.33-4.13) and 6.34 (95%CI: 3.10-9.58) compared to the group without thickening. These reports indicate ultrasonography is useful not only for diagnosis of FH, but also for assessing the risk of cardiovascular events. Even if Achilles tendon thickening is not present at the time of FH diagnosis, lipid accumulation in the tendon progresses over time, making it advisable to measure Achilles tendon thickness periodically. Measurement of the Achilles tendon by ultrasonography is simple, has no X-ray exposure, and can be performed multiple times.

When the Achilles tendon is thickened, it indicates a significant accumulation of lipids within the tissue, highlighting the importance of strict risk management. On the other hand, cardiovascular events can still occur in patients without Achilles tendon thickening. This is particularly true in younger individuals and women, where Achilles tendon thickening may not be evident. Therefore, it is advisable to perform carotid ultrasonography as an additional evaluation, and if atherosclerotic changes are detected, further assessment with coronary CT or coronary angiography should be considered.

ACHILLES TENDON SOFTNESS

The Achilles tendon is a collection of fibers covered by a surrounding membrane called the paratenon. In a normal Achilles tendon, the longitudinal ultrasound image shows a white, thin, linear fibrillar pattern. In contrast, the transverse image shows a thin, oval-shaped, hyperechoic pattern that fills the paratenon [Figure 4A]. As mentioned above, the Achilles tendon sustains minor damage due to mechanical stimulation and weight-bearing, and due to marked hyper LDL-cholesterolemia from birth in FH, excess cholesterol accumulates in the Achilles tendon during repair^[48]. As a result, the ultrasound image of the Achilles tendon in FH is hypoechoic and the fibrillar pattern, which indicates fibrous structure, is no longer visible due to thickening [Figure 4B]. However, in younger patients whose lipid deposition in the Achilles tendon is not yet sufficient for thickening, the diagnosis of FH may be difficult because the Achilles tendon shows hypoechoic areas but not thickening. We speculated that areas of lipid deposition are softer than normal tissue and measured the softness of Achilles tendons. Since ultrasound elastography provides information on tissue softness, we used it as a method for determining FH patients at the pre-thickening stage, measuring Achilles tendon softness as an indicator of the degree of lipid deposition in the Achilles tendon [Figure 5]. The study included 115 genetically diagnosed heterozygous FH patients and 77 non-FH patients. Ultrasound elastography was used to measure the softness of the Achilles tendon, revealing that the hypoechoic areas with lipid deposition were softer than the areas without deposition, and FH patients had softer tendons compared to non-FH patients^[49]. Furthermore, cutoff values for Achilles tendon softness were calculated, and the diagnostic performance of FH was assessed by considering both tendon thickness and softness. When the cutoff values for ATT, EI, and the combination of ATT and EI were applied, the sensitivities were 0.722, 0.670, and 0.817, the specificities were 0.961, 0.883, and 0.844, the positive predictive values were 0.965, 0.895, and 0.887, and the negative predictive values were 0.698, 0.642, and 0.756, respectively, demonstrating improved diagnostic accuracy. Like thickness, softness of the Achilles tendon is shown to be useful in relation to atherosclerosis and in risk assessment for cardiovascular events^[50]. In this regard, a retrospective cohort study found that increased softness of the tendon, which reflects a greater amount of lipid deposition, was associated with increased intima-media thickness and a higher risk of developing cardiovascular events^[47]. There are two types of ultrasound elastography: strain elastography and

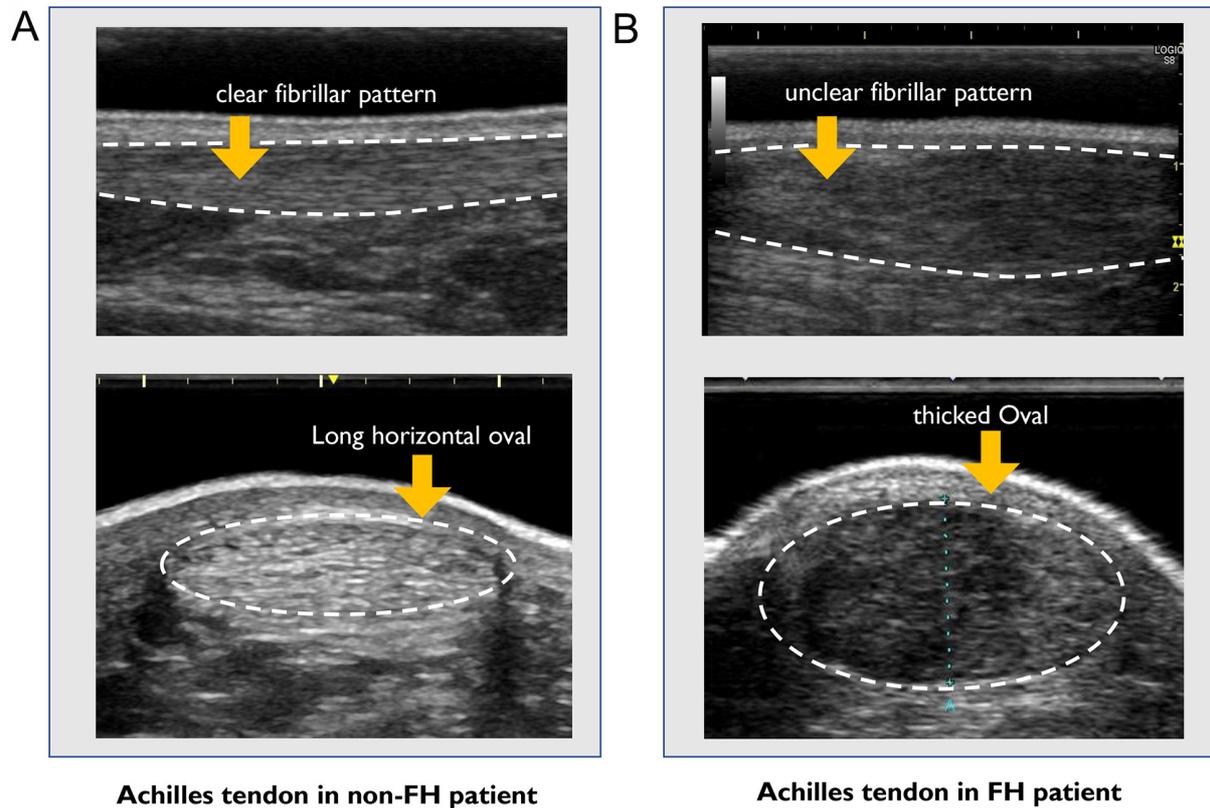


Figure 4. Horizontal and sagittal sonographic appearance of Achilles tendon. (A) sonographic appearance of the Achilles tendon for a 48-year-old male non-FH patient; (B) sonographic appearance of the Achilles tendon for a 24-year-old male FH patient.

shear wave elastography. However, a major issue is that the method of applying the push pulse varies between manufacturers, making it difficult to standardize cutoff values. Standardization across devices is desirable in the future.

ACHILLES TENDON AND FH CAUSATIVE GENES

Approximately 30%-50% of patients with FH do not have thickened Achilles tendons^[24,51], and the degree of thickening varies, suggesting that not only the amount of accumulation of LDL-C, but also the cholesterol efflux capacity of HDL^[52] and other factors are involved in Achilles tendon thickening. FH-causing genes are also involved in thickening, and Achilles tendons are more likely to thicken when mutations in FH-causing genes are present^[13,53]. In particular, patients with mutations in the *LDLR* gene are more likely to have thickened Achilles tendons, whereas *PCSK9* gain-of-function mutations have little effect on Achilles tendon thickening^[13]. However, in compound heterozygotes with *LDLR* mutations and *PCSK9* gain-of-function mutations, the degree of Achilles tendon thickening is greater than for *LDLR* gene mutations alone^[13].

CALCIFICATION OF ACHILLES TENDON

We frequently observe calcification of the Achilles tendon in FH patients with marked AT thickening [Figure 6]. Although Achilles tendon thickening and atherosclerosis are pathologically similar^[54], we have found that calcification is present in patients with FH only on the side with a history of Achilles tendon rupture and therefore, the calcification may be a post-tear scar. However, the presence of calcification in the Achilles tendon is a risk factor for CAD, as compared to FH patients without calcification in the Achilles tendon. We conducted a retrospective cohort study involving 391 clinically diagnosed FH patients over a

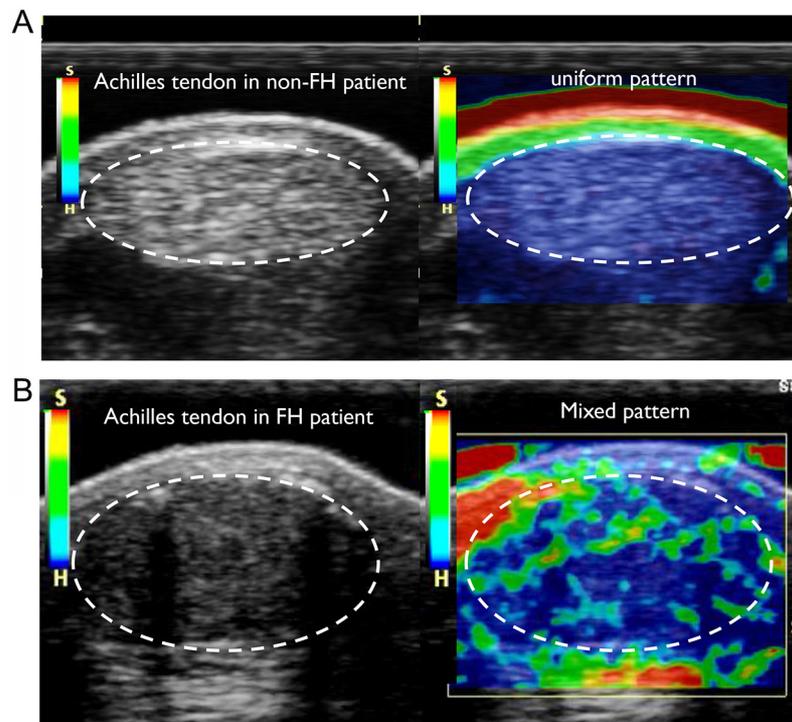


Figure 5. Achilles tendon Ultrasonogram and Elastography. (A) Ultrasonogram and elastogram of the Achilles tendon for a 48-year-old male non-FH patient; (B) Ultrasonogram and elastogram of the Achilles tendon for a 24-year-old male FH patient.

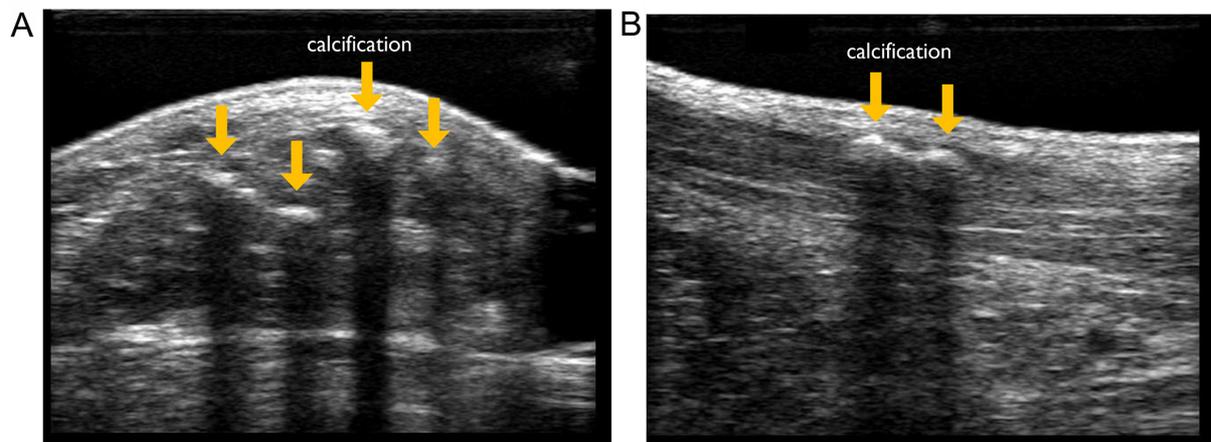


Figure 6. Ultrasonogram of Achilles tendon calcification for patient with familial hypercholesterolemia. (A) Horizontal sonographic appearance; (B) Sagittal sonographic appearance.

period of 1,239 days (700-1,827 days) to assess the risk of MACEs in patients with Achilles tendon calcification. The results showed that patients with calcification had a significantly higher incidence of events compared to those without calcification (OR: 3.66)^[47].

PROSPECTS AND CHALLENGES

Achilles tendon thickening is a characteristic physical finding of FH; however, it is very hard to detect Achilles tendon thickening by palpation^[23]. In order to improve the diagnostic rate of FH, the Achilles

tendon thickness should be measured by ultrasonography or radiography in addition to palpation. We expect the objective assessment of Achilles tendon thickness to be used as a clinical diagnostic criterion worldwide. Ultrasonography can solve the problems of Achilles tendon twisting and X-ray exposure, but there is insufficient evidence for this new method of measurement, so further research, including a large prospective cohort study, is needed. Additionally, since the thickening of the Achilles tendon increases the risk of cardiovascular events, we need to verify whether aggressive LDL-C lowering therapy can improve the prognosis of patients with thickened Achilles tendons. We also need to address the question of whether LDL-C targets should be set even lower in patients with thickened Achilles tendons, even if they are primary prevention patients. Recently, the availability of molecularly targeted therapies, such as PCSK9 inhibitors in heterozygous and homozygous FH and MTP inhibitors and ANGPTL3 inhibitors in homozygous FH, has enabled dramatic reductions in LDL-C. These drugs reduce the accumulation of lipids in the Achilles tendon, which may lead to a reassessment of reference values in the future. We have to clarify whether Achilles tendon thickness normalizes with LDL-C-lowering therapies and the potential role of new pharmacological interventions. Finally, the current reference values for Achilles tendon thickness are for adults (aged 15 years and older), so establishing reference values for those younger than 15 years is urgently required. Although it is difficult to establish reference values for childhood due to the large individual differences in physique, this is an important issue that needs to be resolved for early diagnosis.

CONCLUSION

Achilles tendon thickening is specific for FH and measurement of Achilles tendon thickness and softness is useful not only for diagnosis of FH but also for cardiovascular event risk assessment. Ultrasonography is particularly accurate because it is unaffected by Achilles tendon torsion and can be repeated as it overcomes the problem of X-ray exposure. It is hoped that the measurement of Achilles tendon thickness will improve diagnostic performance and lead to earlier diagnosis and reduced incidence of coronary artery disease worldwide.

DECLARATIONS

Authors' contributions

Conceptualization, writing - original draft: Michikura M
Writing - review & editing: Hoshiga M, Harada-Shiba M

Availability of data and materials

Not applicable.

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Conflicts of interest

Harada-Shiba M is an Editorial Board member of the journal *Rare Disease and Orphan Drugs Journal*. Harada-Shiba M was not involved in any steps of editorial processing, notably including reviewer selection, manuscript handling, and decision making, while the other authors have declared that they have no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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