

Are Neovessels Exclusive to Achilles Tendinopathy Patients?

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Abstract

The response to treatment of Achilles tendinopathy patients is inconsistent. The inconsistency may relate to vascular factors in the tendon. Power Doppler ultrasound scanning is used to assess for the presence of neovascularisation in patients with a chronic mid body Achilles tendinopathy. The relevance of the vessels in the pathology remains unclear. Clinicians are unsure whether they are a positive or negative feature of the pathology.

The primary aim of this study was to determine if the vessels are exclusive to tendinopathy tendons with a view to understanding the pathophysiology. To facilitate this it was necessary to establish the reliability of the methods used to identify and count neovessels.

35 subjects with (n = 37 tendons) and without (n = 33 tendons) an Achilles tendinopathy were assessed for the presence or absence of neovascularisation using Doppler ultrasound scanning. The number of vessels present was documented using the Ohberg score.

The intra-observer reliability of the neovessel score demonstrated 'good' strength (Kappa = 0.69). One tendon out of 33 without a tendinopathy had vessels and 12 tendons out of 37 tendons with a tendinopathy had vessels present.

The identification of neovessels was found to be reliable. Neovessels were found to be almost exclusive to tendinopathy patients, but not all tendinopathy patients had vessels present. This suggests that neovessel proliferation is implicated in the pathology of Achilles tendinopathy but the exact role remains uncertain.

Keywords: Neovessels; Achilles Tendinopathy

Introduction

Despite the prevalence and consequences of Achilles tendon pain, the aetiology and pathogenesis of Achilles tendinopathy remains unclear. In a chronic non-insertional Achilles tendinopathy, structural changes within the tendon can be detected using Ultrasound imaging. Ultrasound scan (US) findings typically seen in tendinopathy are hypoechogenic areas within the substance of the tendon (thought to represent areas of oedema and micro tears), increased tendon thickening, fluid/oedema in the paratenon, calcification, and disarray of collagen fibres with loss of normal parallel arrangement. Ultrasonography is now widely used for the assessment of Achilles tendinopathy [1].

In the last decade, the addition of Power Doppler imaging has enabled detection of blood flow within small vessels in tendons, including detection of blood flow from deep within tissues even when the vessels are too small to see with spectral Ultrasound [2]. Additional, potentially important, information about tendon abnormalities can be provided [3,4].

Neovascularisation (i.e. angiogenesis growth of new vessels from existing vessels) within the Achilles tendon can be detected by Power Doppler ultrasonography (PDU). Neovessels have been observed frequently in patients with chronic mid portion Achilles tendinopathy [3,5-7]. The relevance of this finding is unclear. Based on histological analyses, it has been speculated that the increased vascularisation that is often seen in biopsies might be part of the reparative response in the tendon. In contrast, it has been suggested by some that the invasion and proliferation of new blood vessels may be a contributory factor to the chronic pain associated with an Achilles tendinopathy [8].

A reason for the disparity may be the lack of a uniform method for assessing the degree of neovascularisation. Some studies describe only the presence and absence of neovessels [3,9], others use a scoring system ranging from 0-3 or 0 to 4+ and others use surface area measurements [6,7].

In addition, the reliability of neovessel assessment with Ultrasound has not been fully evaluated. To date only one previous study has examined the reliability of power Doppler measurement of neovascularisation Achilles tendinopathy [10]. Excellent inter observer reliability was found for determining the degree of neovascularisation on PDU (Kappa = 0.85). To the authors knowledge no study has evaluated the intra-observer reliability of neovessel counts.

Aim of the Study

The aims of this study were:

- (a) To determine if neovessels are exclusive to tendinopathy patients.
- (b) To evaluate the intra observer reliability of Ultrasound measurements for quantifying neovascularisation.

Methods

Clinically symptomatic Achilles tendinopathy subjects complaining of pain for 3 months or more and had pain on palpation of the mid body of the tendon. Asymptomatic controls not complaining of pain on palpation of the tendon were recruited from colleagues and the non painful limb of patients with a unilateral Achilles tendinopathy [11].

To determine the prevalence of neovessels and to measure intra-observer reliability, all subjects were scanned for ultrasound evidence of an Achilles tendinopathy. Diagnosis of an Achilles tendinopathy was made on the basis of findings of hypoechoogenic areas within the substance of the tendon, expansion of the tendon and disarray of collagen fibres [1,12,13].

Ethical approval for the study was obtained from South and West Wales Research and Ethics Committee and Research and Development department of ABM Trust (10/WMW02/16).

To determine the presence or absence of a tendinopathy, an ultrasound examination was conducted with the participant lying in the prone position with their feet positioned over the end of the examination couch. Both Achilles tendons were scanned by the same a Consultant Radiologist using an ultra sound scanner (Toshiba Aplio 80, power Doppler 3.1 MHz, using a 8 Mhz linear probe). Ultrasound gel was applied to the Achilles tendon region and both Achilles tendons were examined in the longitudinal (sagittal) and transverse planes from the calcaneal insertion to the myotendinous junction; assessing the tendon for potential tendinopathy and measuring maximum diameters (Figure 1 and 2).

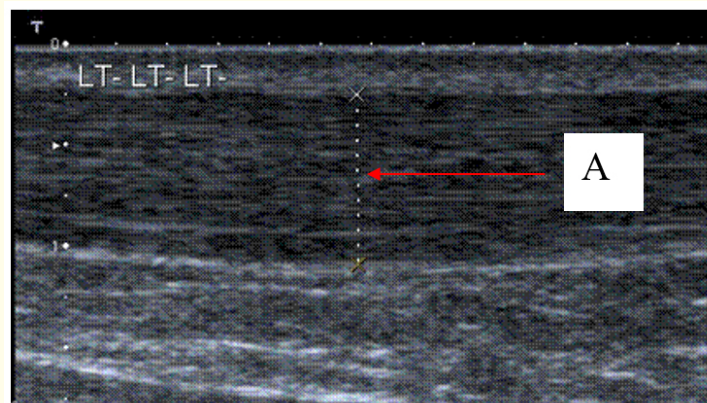


Figure 1: Ultrasound examination longitudinal view of the Achilles tendon demonstrating mild fusiform thickening with anterior posterior diameter electronic caliper measurement. A = Anterior posterior diameter caliper measurement.

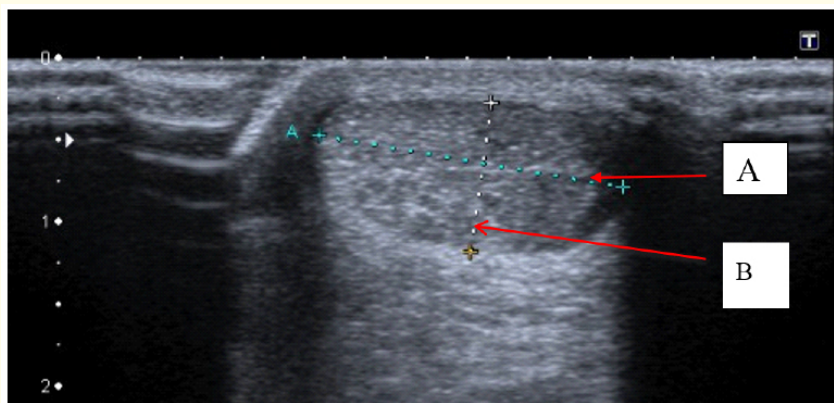


Figure 2: Ultrasound examination transverse view demonstrating the maximum anterior -posterior and mediolateral diameter measurements. A - Mediolateral (coronal) diameter electronic calliper measurement. B - Anterior -posterior diameter electronic caliper measurement.

Power Doppler Ultrasound scanning was then used to detect the presence or absence of vessels in both the patients with and without an Achilles tendinopathy. In patients with ultrasound evidence of a midbody Achilles tendinopathy a standardised computerised rectangular template was positioned electronically using a track ball on the area of tendinopathy. A standardised set of preset parameters was devised (See appendix 1) and used on all subjects for the assessment of the Achilles neovascularity. The standardised template was used to assess the presence and absence of neovessels within that specific area. This area measured 3.5 cm in superior/inferior diameter and 1.7 cm in anterior/posterior diameter (Figure 3). This template area annotated as the “Region of Interest” (ROI) on Ultrasound machines, was kept constant throughout the study.

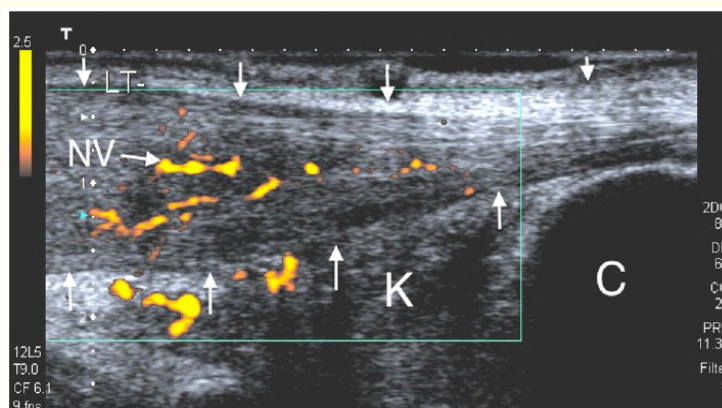


Figure 3: Longitudinal Ultrasound image of left Achilles tendon. Demonstrates use of standardized template for Power Doppler Ultrasound assessment of neovessels - neovessel score: 4. Note fusiform thickening of the Achilles tendon with oedematous paratenon (outlined by arrows), Green rectangle= Region of interest (ROI), NV= Neovessel, K= Kagers fat pad, C= Calcaneus.

The sensitivity and gain factors were standardised and incorporated into a standard pre set, which was used on every subject. The template was placed on the inferior part of the Achilles tendon with the lower inferior margin at the superior border of the calcaneus. A sweep through the tendon was then performed moving medial to lateral with the probe held longitudinally. When the maximum number

of vessels was identified on Power Doppler imaging, an image was taken and the number of neovessels counted and recorded according to the scoring system (Table 1).

Neovascularisation score	Definition
0	No vessels visible
1+	One vessel mostly in the anterior part of the tendon
2	Two vessels within the tendon ROI
3	Three vessels within the tendon ROI
4+	Four or more vessels

Table 1: Interpretation of neovessel score [7,14].

Movement artefact on Power Doppler can produce false positive scores, so the operator observed over a typical acquisition phase of 10 - 15 seconds. Discrete vessels were counted. If one segment of vessel was identified in continuity with another segment it was counted as a single vessel. Structures that were identified as vessels had to be linear structures that demonstrated pulsatility on PDU, with awareness that movement artefact often causes areas of linear colour enhancement. Use of a standard preset that had the pulse repetition frequency (PRF) set for maximum sensitivity at the depth of the Achilles tendon facilitated detection. It is also important to use the appropriately wall filter which reduces artefact from peak systolic flow within vessels. This in combination with the appropriate PRF setting reduces the “bleeding” artefact that is often seen on Power Doppler imaging, which results in a fluorescence like appearance to vessels with marked colour “washout” on detected vessels.

Other relevant Ultrasound factors that enhance sensitivity for neovessels include choosing a low frame rate (9fps used) and reducing the velocity range (we used 2.5 cm/sec in our preset) for detected velocity in vessels on Power Doppler. In the Colour gain setting we used a low setting of 26 (normal range 0 - 80) which enhances sensitivity while reducing artefact due to motion.

Consideration was given to the fact that Power Doppler fundamentally differs from Colour flow imaging in that it detects motion (typically displayed as a monochrome orange colour scale) whereas Colour flow imaging depicts the direction of motion which is displayed as two colours (typically red if flow is directed towards the probe/transducer and blue when flow/movement is directed away from the probe). Thus, Power Doppler Ultrasound is a more sensitive modality for the detection of small vessels compared to colour flow imaging that relies on the detection of direction of movement of blood within a vessel.

In order to assess reliability repeated measurements were conducted in an identical manner approximately 2 hours later. The same treatment room, treatment bed, assessors and ultra sound-scanning machine were used. To reduce experimental bias [15] such as the measurer remembering the first measurements to predict the second, the sequence in which the subjects were seen for the second measurements was randomised.

Data analysis

The Kappa coefficient was used to assess the intra-observer agreement for the neovessel scores. Descriptive analysis was used to determine the prevalence of neovessels in the tendinopathy and non tendinopathy tendons. The analysis was performed using the Social Science Software SPSS (version 13.0) by an independent statistician (OB) and the researcher (AMH).

Results

The sample comprised 35 patients, of whom 69% (24/35) are symptomatic in at least one leg. Measurements are taken from both legs from each patient giving a total sample size of 70 tendons. Of these 70 tendons ultrasound scanning showed that 47% (37/70) were normal and 53% (33/70) were diagnosed as having tendinopathy. The sample were predominantly male (21/35) and had a mean (SD) age of 50.5 (9.5).

There is a significant association between symptoms and the presence of tendinopathy (p < 0.001; Chi-Square). Of those with symptoms, the majority have tendinopathy (78%, 28/36) while the converse is true for non-symptomatic tendons (27%, 9/34).

Only a small proportion of patients show signs of neovessels (19%, 13/70). However the prevalence is significantly higher ($p < 0.002$; chi-square) among patients with tendinopathy, with a 32% (12/37) of diseased tendons having neovessels compared to only 3% (1/33) of healthy tendons. This suggests a very strong connection between tendinopathy and neovessels. A full breakdown of neovessel, broken down by tendinopathy status and the presence or absence of symptoms, is given in table 2.

Ultrasound scan for tendinopathy	Positive (N = 37)		Negative (N = 33)	
	Present	Absent	Present	Absent
Neovessels?				
Symptomatic tendon (N = 36)	11	17	1	7
Asymptomatic tendons (N = 34)	1	8	0	25

Table 2: The presence and absence of neovessels in tendons with and without an achilles tendinopathy.

The primary research focus on this study is the reliability of measurements of neovessels. At the simplest level the presence or absence shows a high level of intra-rater reliability (Kappa = 0.811 [0.629, 0.993]) which is generally classified as a ‘strong’ level of agreement. This corresponds to 94% agreement between the two ratings. When we consider instead the measurement of the number of neovessels (as opposed to the binary measure of their existence) the level of agreement falls slightly, to ‘moderate’ (0.694 [0.500, 0.888]) but still represents a 90% agreement between assessments.

Discussion

The intra-observer reliability of the neovessels score in this study was found to be good. Whilst this is the first study evaluating the intra-reliability of neovessels measurements, the intra-reliability was found to be lower than the inter-reliability measurements found in Sengkerij, *et al.* 2009 study [10], where the reliability was 0.85 (Kappa). The higher inter-reliability found by Sengkerij, *et al.* 2009 [10] may have been because the patients remained in the same position and a second radiologist conducted the scan. In our study patients returned for the second scan 2 hours after the initial scan.

In this study neovessels were found to be almost exclusive to tendinopathy patients but not all the tendinopathy patients demonstrated neovessels. This supports the findings of Peers., *et al.* 2003, Reiter 2004 and Zanetti, 2003 [9,16,17] but in contrast to the findings of Ohberg., *et al.* 2001 [3] who found neovessels in all tendinopathy patients.

The exact relationship between the physiology of an Achilles tendinopathy and severity of symptoms therefore remains unclear. Further studies should consider evaluating changes in neovessels at regular intervals over the duration of the clinical episode. This may help improve our understanding of the timing of the development of neovessels. It is possible that these are related to certain phases of the healing process, a flare up of the condition or simply a response to the patient’s level of activity that day.

Conclusion

This study found that neovessels are almost exclusive to tendinopathy patients, although not all tendinopathy patients have neovessels and the intra-observer measurements of a neovessel score to be reliable. The interpretation of the findings of angiogenesis and their relevance to the natural history of Achilles tendinopathy need further evaluation.

Acknowledgements

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Appendix 1

Ultrasound preset used for the detection of Neovessels.

ROI 3.5cm x 1.7cm.

Probe 12 L5 - 9MHz frequency.

Colour Flow (velocity range) 2.5 cms/sec

Frame rate 9 fps.

Overall grey scale gain 2 DG 85.

Dynamic range - 65 (standard dynamic range)

Colour Gain 26 (range 0 - 80)

Pulse repetition frequency (PRF) 11.3 Mhz

Filter 5 (Wall thump filter).

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