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EDITORIAL

Neovascularization in Achilles tendinopathy: have we been chasing a red herring?

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Abstract The concept of neovascularization in tendinopathy seems to have gained nearly mythological proportions and quasi-religious state: it is considered of diagnostic and prognostic value, related to clinical outcome, and the exclusive target of some therapeutic interventions. However, we question whether these assumptions are based on scientific evidence, and we come to the conclusion that, in the light of recent well-performed research, it seems that detecting neovessels has no additional value for the diagnosis, no firmly confirmed prognostic value, and no proven relation with symptoms. The role of neovascularization in this field should be re-thought. *Level of evidence* V.

Keywords Neovascularization · Achilles tendons · Power Doppler · Color Doppler

'How often have I said to you that when you have eliminated the impossible, whatever remains, *however, improbable*, must be the truth?' said the most famous consulting detective of the literature, Sherlock Holmes, to Doctor Watson [17]. The same logically strict deductive process should be applied to neovascularization in Achilles tendinopathy [34, 35]. Indeed, in some quarters, the concept of neovascularization in tendinopathy seems to have gained nearly mythological proportions and quasi-religious state: it is considered of diagnostic and prognostic value, related to clinical outcome, and the exclusive target of some therapeutic interventions. However, are these assumptions based on scientific evidence, or are they as vulnerable as Achilles' heel, eventually punctured by Paris' killing arrow?

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Historical perspective

Until recently, doctors' status was unquestioned, and patients fully trusted their opinion. At present, we have to substantiate our diagnoses with (novel) imaging modalities, even when the clinical picture is clear. In the 1990s, blood flow in symptomatic tendons on power Doppler ultrasonography (PDU) was firstly described by Newman et al. [36]. Subsequently, two Scandinavian colleagues, Ohberg and Alfredson [38], defined this blood flow as 'neovascularization'. The blood vessels were thought to be formed anew and were described as tortuous vessels with a small lumen, predominantly located on the anterior aspect of the Achilles tendon, infiltrating it diffusely. From an etiological perspective, the neovessels were thought to be secondary to the essential abnormality of tendinopathy, the failed healing lesion [10].

Using color Doppler ultrasound (CDU), Öhberg and Alfredson showed, in a case–control study, increased blood flow and neovascularity in all painful tendons and absence of these features in the asymptomatic control tendons [2].

They described a five grade ultrasonographic neovascularization score, which has excellent reliability [44].

Histopathology

Healthy tendons are relatively avascular [45]. Recently, neovascularization and the accompanying neonerves have been hypothesized to be the source of pain in chronic mid-portion Achilles tendinopathy [3, 23, 27, 46, 47, 50, 53]. This hypothesis was advanced after the detection of several sensory neurotransmitters within and around the tendons using microdialysis [24] and staining of pathologic tissue specimens. Also, in the area of neovessels, there are more sympathetic than sensory nerves, with pronounced occurrence of α-adrenoreceptors, which mediate vasoconstriction. In asymptomatic tendons, there may be a physiologically slow blood flow that cannot be detected with PDU. In tendinopathic tendons, Andersson et al. [3] hypothesized that the induced vasoconstriction might lead to increased blood flow, which can be detectable by ultrasonographic Doppler techniques [19].

To the best of our knowledge, the appearance of such vasculo-neural ingrowth has only been studied once in Achilles tendinopathy, without specifying the number of observed nerves, exact relation to the neovessels, reversibility, nor their existence in asymptomatic tendons [3, 35, 43]. Biopsies form tendinopathic patellar tendons have shown increased avascular sensory nerves and decreased vascular sympathetic nerves [25].

Diagnosis

The diagnosis of Achilles tendinopathy is clinical, with pain, swelling, and impaired performance as the cardinal signs [22, 28, 30]. Symptomatic tendinopathic Achilles tendons with neovascularization show evidence of a statistically significant association between site of maximum tenderness on palpation and site of maximum presence of PDU neovessels [16]. It is, however, unknown whether the degree of maximum pain is associated with the degree of neovascularization.

In patients with a clinical diagnosis of Achilles tendinopathy, there is conflicting evidence about the presence of neovessels. In the Swedish studies, the investigators were able to detect neovessels in 100 % of the symptomatic tendons [1, 26, 37, 38]. This observation was not supported by other researchers, who reported a percentage varying from 47 to 88 % [13, 41, 42, 54].

Also, neovessels were detected in 29 % of asymptomatic athletes [44], and in 100 % of subjects after strenuous exercise [6]. Therefore, are these neovessels really newly formed blood vessels, and does neovascularity reflect a physiological or a pathological response?

Reviewing these studies, a limitation might be the lack of standardization in assessing the degree of neovascularization and degree of prior physical activity [6]. In a cross-sectional study in active athletes, Doppler flow was not associated with pain but might reflect an adaptation to mechanical load [35].

Relation with clinical severity

Only a few studies have examined the association between neovascularization and pain or function. Reiter et al. [42] identified a statistically significant association between the presence of neovascularization and pain and restricted function in 20 patients, but de Vos et al. [13] and Sengkerije et al. [44] found no relation between degree of neovascularization and pain or VISA-A [31] score in 63 tendons [13]. As in both these studies the power calculation was not based on change of neovascularization score, no definitive conclusion could be drawn.

More recently, a prospective study with over 500 coupled measurements showed no evidence of an association between neovascularization and pain domain of the VISA-A score. This study also confirmed the earlier findings of absence of correlation between the neovessels and overall VISA-A clinical outcome score [48].

Prognosis

The predictive value of neovascularization has been studied by Zanetti et al., using only a VAS and not a functional score [54]. Nevertheless, these authors reported that the presence of neovascularization at baseline had no role in predicting outcome after three and 6 months.

These findings were confirmed by de Vos et al. [13], who showed that neovascularization at baseline did not predict outcome in patients treated with the Alfredson eccentric exercises [32, 39]. In a recent larger series, it was also confirmed that a reduction from baseline neovascularization is not associated with improvement of VISA-A or decrease of VAS pain score [48].

Neovessels and therapeutic interventions

Several conservative and surgical interventions target neovessel destruction as the key to success. The most direct approach utilizes sclerosing injections of polidocanol. The original promising results have not [51], however, been confirmed in an independent large retrospective series [49].

Another injection modality that targets the area of neovascularization is high volume image guided injections (HVIGI) [11, 20, 21]. In a relatively small cohort of patients, this therapy improved the short-term functional outcome and reduced the neovascularization score, though there was no significant association between a decrease of the neuro-vascular ingrowth and functional outcome [9, 11, 21].

The potential effect of PRP on neovessels has only been studied once in Achilles tendinopathy [4, 5, 8, 12, 14, 15, 29, 40]. It is hypothesized that the formation of neovessels is related to the release of vascular endothelial growth factor (VEGF), a potent stimulator of angiogenesis [7]. VEGF is also released after injection of platelet rich plasma (PRP). An initial increase of neovascularization after PRP injection was indeed reported, but did not differ from what occurred after placebo injection of saline, suggesting a needle instead of content effect [14].

The Achilles heel

The introduction and popularization of the neovascularization theory has given an enormous stimulus to Achilles tendinopathy research. With the increase in number and quality of studies, the Achilles heel of this promising theory has become apparent. In the light of recent well-performed research, it seems that detecting neovessels has no additional value for the diagnosis, no firmly confirmed prognostic value, and no proven relation with symptoms [33]. Also, all these issues lack of standardization of machine settings before expanding on the role of the neovascularization itself in the process of tendinopathy [52]. Hence, as Holmes said before, it should be clear that 'It is a capital mistake to theorize before one has data. Insensibly one begins to twist facts to suit theories, instead of theories to suit facts' [18].

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