nature reviews disease primers

https://doi.org/10.1038/s41572-025-00602-9

Primer

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Achilles tendinopathy

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Abstract

Achilles tendon pathologies are prevalent, impacting ~6% of the general population and up to 50% of elite endurance runners over their lifetimes. These conditions substantially affect quality of life and work productivity, leading to substantial societal costs. Achilles tendinopathy (AT) is a condition marked by localized pain and functional impairment related to mechanical loading. AT can considerably impair participation and potentially also performance in sports and daily activities. The aetiology of AT is multifactorial and repetitive overloading of the tendon is often observed as the inciting factor by health professionals. However, AT can also be associated with adverse effects of certain medication, ageing and various comorbidities. Characteristic tendon changes include proteoglycan accumulation, fluid accumulation with swelling and hypervascularization. Tissue disorganization advances as pathological changes in matrix structure are driven by altered cellular function and makeup, often accompanied by persistent inflammation. Treatment strategies include various interventions, although these can be protracted and challenging for both patients and health-care providers, often with high failure rates. Current research focuses on understanding the pathological processes at the cellular and molecular levels to distinguish between disease categories and to investigate the role of inflammation, metabolic maladaptation and mechanical stress. Emerging therapeutic approaches need to be developed to address these underlying mechanisms. These approaches focus on optimizing rehabilitation protocols and advancing the development of adjunct therapies, such as advanced therapy medicinal products, alongside the integration of precision medicine to improve treatment outcomes.

Sections

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Introduction

Achilles tendinopathy (AT) is a common and complex disorder affecting the Achilles tendon, the largest and strongest tendon in the human body[1]. AT is prevalent among athletes but also affects the general population. The incidence of AT is approximately 2 cases per 1,000 individuals per year, with much higher rates among athletes[2,3]. AT is a particularly prevalent condition in sports requiring repetitive strain on the tendon, such as running and jumping[4–6]. Many patients with AT experience persistent symptoms for years, often leading to decreased overall physical activity[7–10] (Box 1).

The Achilles tendon (also called the calcaneal or heel tendon) is a robust structure formed by the convergence of the gastrocnemius and soleus tendons inserting into the posterior aspect of the calcaneus (heel bone). The Achilles tendon plays a critical role in plantar flexion of the foot, which is essential for walking, running and jumping[11], and it is surrounded by the peritenon, a two-layer connective sheath consisting of the epitenon and the paratenon. The peritenon serves as a flexible, lubricating structure that facilitates tendon gliding, much like a synovial sheath. Each fascicle of the tendon core is surrounded by the endotenon, also known as the interfascicular matrix[12]. All these connective sheaths are highly cellularized and provide blood supply to the Achilles tendon. In contrast, the Achilles tendon core, particularly the midportion, is characterized by a decreased cellularity and generally low vascularization[13,14]. At the bony insertion site, the Kager fat pad and the retrocalcaneal bursa are located between the bone and tendon to reduce friction during movement and to support mechanical function[15] (Fig. 1).

Box 1 Defining features of AT

Achilles tendinopathy (AT) refers to a spectrum of tendon disorders and is characterized by pain during physical activity, focal tenderness upon palpation, potential swelling of the tendon and a negative impact on participation and performance in sports and daily life.

Overuse

AT predominantly results from repetitive mechanical stress (for example, training with too much intensity or volume) that involves the tendon elastic function and results in tendon-related symptoms.

Morphological tendon tissue changes

AT is characterized by increased proteoglycan deposition, swelling and hypervascularization, and by tissue disorganization. Both altered cell function and composition in combination with altered matrix structure with changes in the fibrillar matrix and signs of unresolved inflammation are typical features of AT.

Subclassification

Based on anatomical location, insertional and midportion AT are differentiated. Further classification based on symptom duration is inconsistent in the literature and is not further addressed.

Secondary AT

In these cases, AT is caused by conditions other than repetitive mechanical overload, such as medication side effects or comorbidities.

Healthy tendons are bradytrophic, characterized by a slow metabolism, and are relatively hypocellular compared with other tissues. Despite their low cell density, tendons contain a heterogeneous population of cells with distinct functions[16–18]. The most abundant cells in the tendon are the matrix-producing fibroblast-like tenocytes, which are primarily responsible for synthesizing and maintaining the extracellular matrix (ECM), particularly type I collagen — the key structural protein that provides tensile strength. Additionally, multipotent tendon stem or progenitor cells (TSPCs) have been identified in tendons and are likely to be critical for tendon homeostasis and healing[19]. Tendons further harbour a relatively sparse population of endothelial cells and tissue-resident immune cells, including macrophages and T cells. However, a unified classification system for tendon-resident cells and their progenitors is yet to be established.

The aetiology of AT remains a topic of debate and is influenced by a combination of intrinsic factors and extrinsic factors[20–22]. AT is characterized by pain, functional impairment, frequently related to mechanical loading, and potential tendon swelling, often resulting from overuse, with symptoms frequently failing to fully resolve[20,21]. Historically, 'tendinitis' was used to describe tendon pain, swelling and impaired function. However, these terms — along with 'tenosynovitis' and 'tendinosis' — are now discouraged, as they suggest specific pathological processes that cannot be reliably assessed in clinical practice[21,23,24]. The pathophysiology of AT is marked by degenerative changes in the tendon matrix, which compromise its mechanical properties. These changes include collagen disorganization, proteoglycan accumulation and hypervascularization. AT is traditionally divided into insertional and midportion (also known as non-insertional) tendinopathies. Insertional tendinopathy affects the area where the tendon inserts into the calcaneus. By contrast, midportion tendinopathy occurs ~2–7 cm proximal to this insertion area[25] (Fig. 1). The condition less commonly affects the musculotendinous junction.

The diagnosis of AT primarily relies on a thorough clinical assessment and patient history. Key diagnostic criteria include pain localized to the Achilles tendon, pain triggered by loading and palpation and, in some cases, local swelling of the tendon[20,26]. Imaging techniques such as ultrasonography and MRI can be used when the diagnosis is uncertain or before treatment, with conventional ultrasonography being the most used.

The management of AT remains challenging owing to its multifactorial causes and complex pathophysiology. Furthermore, robust evidence-based research and a universally accepted gold standard treatment are lacking. Meta-analyses suggest that no single type of loading exercise consistently outperforms others in alleviating pain or enhancing functional capacity[27,28]. However, passive 'wait-and-see' approaches should generally be discouraged, as active treatments have demonstrated superior outcomes[28]. In addition to various loading protocols, adjunct therapies are often employed, yet no consensus is available regarding their prioritization. Surgical intervention is typically considered only after conservative treatments have been attempted without success[29], with options including open and minimally invasive techniques[20,30]. Achieving optimal outcomes depends on accurate diagnosis, personalized treatment plans and comprehensive patient education. However, the prognosis varies widely, with some cases resolving within weeks, whereas others may take months or even years, and a proportion of patients fail to achieve full resolution.

In this Primer, we review epidemiology, diagnosis, management and the latest advances in our understanding of AT. Additionally, we discuss the diminished quality of life of patients as well as aim to synthesize

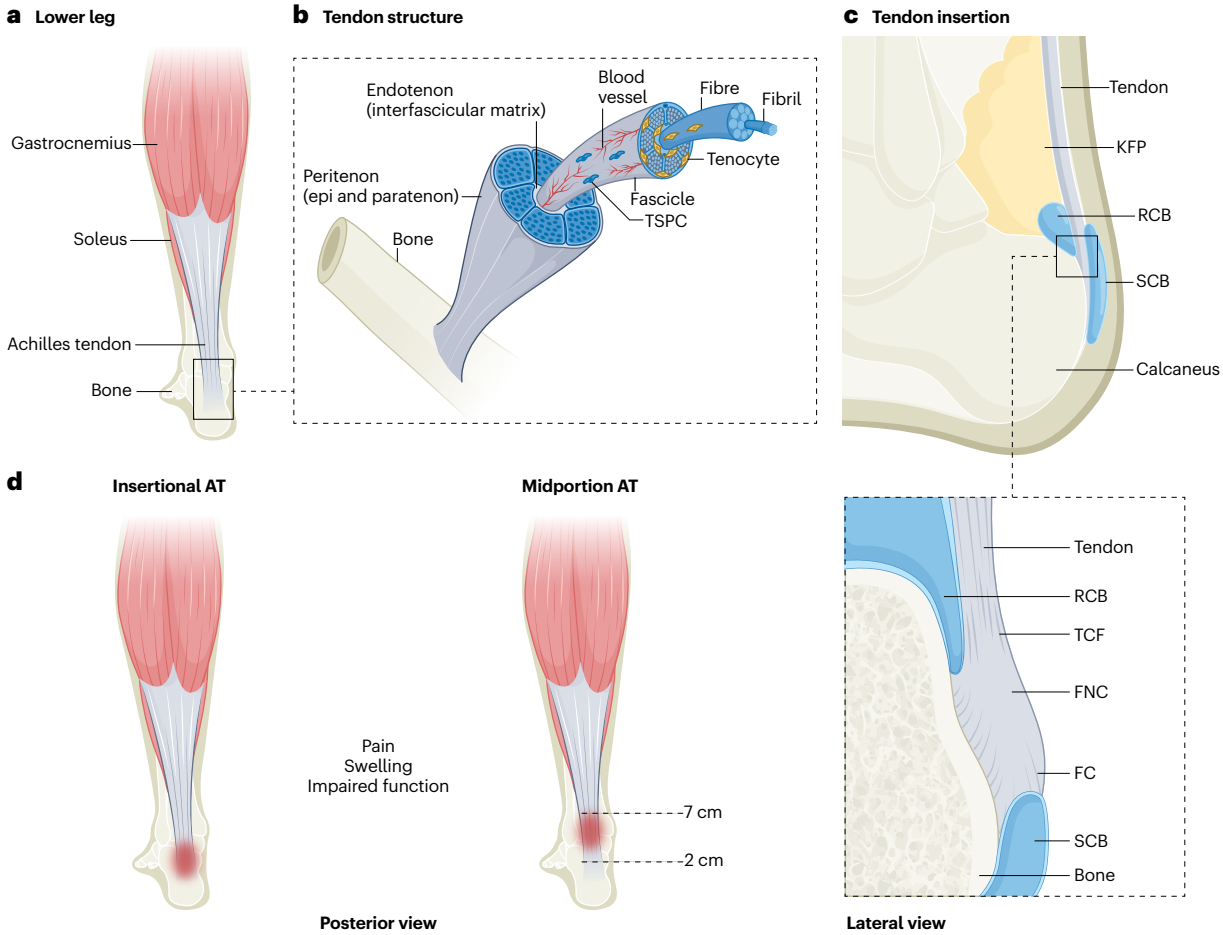

Fig. 1 | Achilles tendon structure and tendinopathy. a, The Achilles tendon connects the calcaneus (heel bone) to the gastrocnemius and soleus muscles of the lower leg (posterior view). **b**, The primary extracellular component of the tendon is type I collagen, which is organized hierarchically into fibrils, fibres and fascicles, surrounded by the interfascicular matrix, also known as the endotenon. The tendon contains tendon fibroblasts (tenocytes), multipotent tendon stromal stem or progenitor cells (TSPCs), and other tendon-resident cells (not depicted). **c**, The retrocalcaneal bursa (RCB), the subcutaneous calcaneal bursa (SCB) and the Karger fat pad (KFP) contribute to gliding and/or shock absorption, protecting the tendon from mechanical stress. The tendon is anchored to the calcaneal tuberosity via a fibrocartilaginous enthesis, a specialized structure comprised of layers of tendon connective tissue (TCF), non-calcified fibrocartilage (FNC), calcified fibrocartilage (FC) and bone (lateral view). **d**, Insertional tendinopathy affects the tendon near the enthesis, whereas midportion tendinopathy affects the central aspect of the tendon. AT, Achilles tendinopathy.

and interpret the existing gaps in knowledge and propose strategies to overcome these challenges to enhance patient outcomes.

Epidemiology

Prevalence

Overuse of the Achilles tendon is one of the most frequent tendon injuries, occurring in relation to occupation or leisure time activity, and affecting the general population as well as recreational and competitive level athletes. Whereas ~6% of the general population will experience AT during their lifetime, >50% of all elite distance runners will have a period with AT during their life[31] (Table 1). AT is the most prevalent tendinopathy affecting the lower extremities in the general population – excluding plantar fasciopathy, which is not typically classified as a classic tendinopathy. AT is also the most common tendinopathy in physically active individuals, followed by patellar tendinopathy[3]. In competitive track and field athletes, AT is the second most frequent injury overall (secondary to acute muscle strain injury) in relation to the amount of time lost from sports owing to injury[32].

Incidence

Whereas the incidence of AT in the general population is ~2 per 1,000 persons per year[2,3,33], the incidence can be as high as 80–100 per 1,000 persons per year in athletic or military populations undergoing continued strenuous loading of the tendon[32,34,35] (Table 1). In running sports, two out of three individuals suffer from AT and the injury is typically localized to the midportion of the Achilles tendon, whereas in a quarter of individuals with AT, the injury will be localized to the Achilles tendon insertion and the remaining 10% of runners will present symptoms at both locations[35].

Table 1 | Frequency of Achilles tendinopathy in populations

Type of individual and country	Frequency	Incidence per 1,000 persons per year	Ref.
General population			
Finland	Incidence 6% (lifetime)	1.2 (assuming 50 years active life)	31
Netherlands	Incidence not reported	2.2 (mean age 36 years)	33
Netherlands	Incidence not reported	1.84 (2.35 in age range 21–60 years)	2
Denmark	Incidence not reported	1.7 (mean age 39 years)	3
Runners			
Finland	Incidence 52% (lifetime)	52 (assuming 10 years of competitive activity)	31
Netherlands	Incidence 4.2% (>20 weeks)	105 (assuming 50 active weeks per year)	35
Netherlands	Incidence 4–7.4% (>12 months)	74 (mean age 42 years)	42
Competitive track and field athletes			
UK	25 cases (217 athlete-years)	110 (mean age 24 years)	32
Military personnel			
USA	Prevalence 17%	80 (military service duration)	34

Risk factors

AT is a multifactorial condition probably related to an interaction of intrinsic and extrinsic factors that leads to tendon overuse[36]. Systematic reviews have highlighted important risk factors and factors associated with AT[22,37–40]. Male sex[35], older age[41] and prior injury[35,42] are suggested as non-modifiable factors that may increase the risk of AT. However, studies have also described several modifiable factors, which provide clinicians with the possibility to address these factors to prevent a first episode of AT or to decrease the likelihood of recurrence[43].

Prospective studies have suggested that decreased ankle plantar flexion strength[44] and decreased ankle dorsiflexion range of motion[45] are intrinsic risk factors for developing AT. However, some studies have not demonstrated any association between ankle range of motion and the onset of AT[44,46]. Extrinsic factors such as a sudden increase in training volume, having a strict training schedule, occupation, certain sports, intensive training in cold weather, some medications (for example, fluoroquinolones, statins and steroids)[47,48], and alcohol consumption have also been suggested to be risk factors for AT[22,42]. However, increased mechanical loading has never been directly demonstrated to be causative in the development of AT, but the suggestion was derived from correlative studies in which populations with increased mechanical loading of the tendon showed a higher incidence of AT than populations without increased loading. Finally, most cases of AT may be categorized as primary tendinopathy (no known medical cause) and only a minority of AT cases may be considered secondary to another medical condition (for example, tendon xanthoma, diabetes mellitus and medication reaction).

Several other relevant factors have also been associated with AT in cross-sectional studies and may contribute to the persistence of symptoms. These factors include deficits in strength[37], power[40] and endurance[49] of the ankle plantar flexor muscles, deficits in knee extension strength[50], deficits in hip abduction[50,51], hip extension[50,51] and hip external rotation strength[51], and delayed gluteus maximus and gluteus medius activation during running[52]. Given that these muscle groups are important primary motors or stabilizers during functional and sports-related activities (such as walking and running), deficits in these muscles may increase the demand on the Achilles tendon, potentially contributing to overuse.

Psychological factors such as kinesiophobia[53], anxiety, catastrophizing and self-efficacy[54] have also been associated with AT, and should be included in assessments for a thorough, biopsychosocial approach. An important non-modifiable risk factor is prior tendinopathy[22,42], which highlights the importance of prevention of a first episode of AT for long-term tendon health. However, for many of these factors, the evidence is very weak and often only small studies have been undertaken.

Genetics. Besides the aforementioned factors, genetic and metabolic factors have also been linked to the occurrence of AT. Several genetic polymorphisms (that is, single nucleotide variants) have been suggested to be associated with an increased risk of developing AT. For example, variants in *COL5A1* have been consistently associated with an increased risk of AT[55,56]. However, the number of patients in these studies together with the low number of variants studied do not allow any robust conclusions to be drawn. Mechanistically, variants in *COL5A1* could lead to structural changes in type V collagen as demonstrated in patients with Ehlers–Danlos syndrome who have defective collagen and display altered mechanical properties of their tendons[57]. Additionally, a genome-wide association screen of 102,979 individuals (5,418 with AT or rupture, 598 with anterior cruciate ligament rupture) demonstrated only borderline association of four polymorphisms associated with Achilles tendon injury[58], whereas a follow-up study including 3,680 individuals (1,288 with AT) demonstrated that *MMP7*, *TIMP2* and *CASP9* variants are associated with AT[59].

Metabolic disorders and rheumatic diseases. Metabolic conditions such as obesity[38], chronic hyperglycaemia[60], hypercalcaemia, dyslipidaemia and endocrinopathies[47] have also been shown to interfere with tendon homeostasis, potentially increasing the risk of tendinopathy. Elevated glycated haemoglobin (HbA1c) as well as hypercholesterolaemia were associated with twofold to threefold increased risk of developing tendinopathy (secondary tendinopathy)[60]. A cross-sectional study in 111 patients with AT revealed a negative effect on the Achilles tendon if the patient had two or more metabolic risk factors[61]. Surprisingly, intensified systematic management of patients with type 2 diabetes mellitus that included lifestyle advice incorporating increased physical activity, resulted in an increased risk of tendinopathy and tendon rupture, potentially owing to a rapid initiation of physical training leading to overuse of the tendon[62]. Furthermore, clinical examination might reveal symptoms of secondary AT in patients with autoimmune disorders such as rheumatoid arthritis, ankylosing spondyloarthropathy and psoriatic arthritis[63].

Taken together, AT is a frequent condition with midportion AT being the most common type. Important risk factors include high training volume and especially increased training within the months prior to onset of symptoms, as well as a history of previous AT. Moreover, insertional AT can be related to younger age and is often related to developmental growth in a vulnerable site or in adults who have other diseases such as rheumatic or metabolic diseases[64,65].

Mechanisms/pathophysiology

The Achilles tendon is a highly adapted energy storing flexor tendon susceptible to injury. As previously highlighted, the aetiology of AT is complex and multifactorial, encompassing the effects of ageing, genetic factors, and biomechanical and cellular factors[66–68]. Both structural and compositional features of the Achilles tendon predispose to tendinopathy and potentially to subsequent rupture of the tendon midportion or at the enthesis. Achilles tendon ruptures may or may not be directly associated with AT; whether patients with a previous Achilles tendon rupture are at increased risk of developing AT remains a topic of debate. Currently, making a clear distinction between these conditions in terms of the underlying molecular and cellular mechanisms is challenging. Hence, pathophysiological aspects of Achilles tendon rupture are also discussed in this section.

Structure of the Achilles tendon

The Achilles tendon is the strongest tendon in the body and is predominantly composed of parallel type I collagen fibres organized into fascicles of the tendon proper (core), bound by the interfascicular matrix, a loose connective tissue (Fig. 1). Multipotent TSPCs reside within the interfascicular matrix, potentially reflecting an essential role in supporting tissue repair. Biomechanically, the interfascicular matrix is highly specialized in the Achilles tendon, enabling fascicle sliding and capacity for energy storage, demonstrating increased elasticity and fatigue resistance relative to the positional anterior tibial tendon[69]. By contrast, the entheseal region of the Achilles tendon is interfascicular matrix sparse and consists of a transitional zone whereby type I collagen fibres merge into an avascular fibrocartilaginous zone and bone interface[70,71] (Fig. 1). In this section, we discuss the pathobiological mechanisms underpinning the development of midportion AT and insertional AT, with particular focus on the biomechanical, cellular and molecular mechanisms driving the disease.

Biomechanical factors

During activities such as running, the Achilles tendon can bear loads up to more than seven times the individual's body weight[72]. These high tensile forces arise primarily from muscle contractions and ground reaction forces during the push-off phase of gait[72]. The anatomically twisted structure of the Achilles tendon reflects its function in transmitting forces from the medial and lateral heads of the gastrocnemius and the soleus muscles across a wide range of ankle joint motions. This anatomical configuration is crucial for the effective distribution of mechanical forces, subjecting the tendon core to a combination of tensile, compressive and shear stresses[73] (Fig. 2).

Mechanosensing allows cells within the tendon to detect mechanical cues in their environment, whereas mechanotransduction involves the conversion of these mechanical signals into biochemical signals that cells can process. Key mediators of these two processes include ion channels, integrins and cytoskeletal elements, and relayed mechanical signals to the cell nucleus[73,74]. Tendon fibroblasts (tenocytes) in the core are recognized for their role in tendon mechanosensing, regulating the adaptation of a healthy tendon[75]. Additionally, macrophages are mechanosensitive cells that majorly contribute to repair processes in tendons, modulate inflammatory responses and facilitate tissue remodelling[76].

In healthy tendons, mechanosensing is a central element in maintaining tissue homeostasis, guiding cellular behaviours that ensure a functional collagen matrix structure. In tendinopathy, transfer of biophysical cues to cells embedded within a damaged or otherwise deranged ECM disrupts this balance[77,78]. The pathological response that results from aberrant mechanical stimuli in turn affects gene expression and protein synthesis, further affecting tendon structure and function[79–81]. In disease states, a perpetuating cycle of biophysical stimuli and inadequate healing emerges, which drives the progressive loss of collagen fibre orientation and increased cellular activity that characterizes the advance through clinical stages of tendinopathy[21].

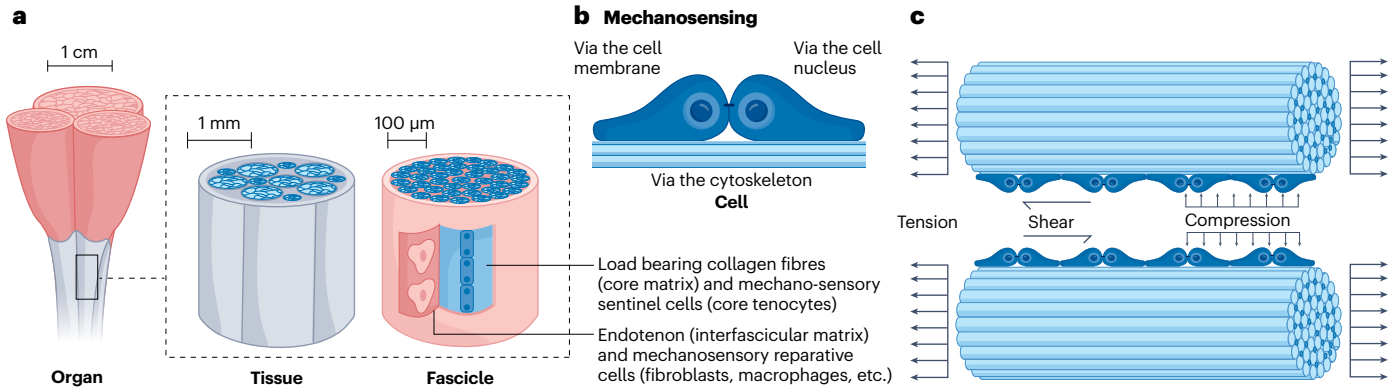

Fig. 2 | Multiscale interplay of structural organization and functional mechanics in tendon tissue. The figure highlights the complex relationship between tendon tissue structure and biomechanical properties. This relationship dictates the emergence of mechanical stresses within the tissue and the evolution of mechanisms by which tendon cells can sense deformations that occur under these stresses. **a**, The tendon's mechanical properties are derived from the molecular organization of collagen into fibres and fascicles, surrounded by a cell-dense interfascicular matrix (endotenon) and encased by the peritenon. This multiscale structural arrangement not only supports robust mechanical function but facilitates cellular 'handshaking' between the load-bearing tendon core and the supportive surrounding stromal tissue. **b**, Mechanical stresses activate various mechanosensory elements within the cells whose activity is gated or potentiated by physical deformation of sensors coupled to the cell membrane, cell cytoskeleton, and/or nucleus. These elements are central in transducing mechanical signals within the tissue to regulate cellular signalling and behaviours essential for tendon function and adaptation. **c**, Stresses in the tendon core, including shear from fluid flow and fibre sliding, tensile stresses from collagen fibre elongation and hydrostatic pressures from compression, are induced by external loading at the organ level. Adapted with permission from ref. 73, Elsevier.

The drivers of aberrant tissue remodelling probably include multiscale mechanical stimuli, unbalanced proteolytic turnover and/or the progressive accumulation of a mechanically inferior ECM with altered ratios of, for example, type I collagen to type III collagen or SPARC[73,81,82]. Regardless of the source of damage, deviations from a tightly packed type I collagen matrix will biomechanically compromise the tissue, impacting the mechanically regulated biological processes of embedded cells. Damage sensing by cells and their biological response depend on the cellular niche, which is determined by factors such as nutrient supply[83] and other biochemical cues, such as the presence of alarmins[84,85] (for example, ECM fragments or high mobility group box 1 protein). These factors are released after injury or during the repair process, which can then initiate or perpetuate inflammatory pathways. Mechanical damage also affects tissue porosity and solid–fluid interactions within the tendon matrix, which in turn can impact cell function and nutrient transport. Cellular alignment with, and confinement by, the normally dense and highly aligned collagen matrix can also be compromised, potentially enabling behaviours that are normally inhibited by confinement such as cell differentiation, migration and/or cell proliferation[86].

AT can manifest in the midportion of the tendon or at its insertion on the calcaneus. Each location is subjected to unique mechanical stresses, which may predispose the tendon to specific pathologies[87]. Midportion tendinopathy is typically linked to tensile overload, resulting in microdamage, whereas insertional tendinopathy often relates to increased shear forces and compressive loads, especially when the ankle is dorsiflexed, such as during uphill running or jumping. These biomechanical forces can exacerbate tissue degeneration and calcification at the insertion site. A thorough understanding of the interplay between biomechanical stresses and cellular responses in AT is vital for developing targeted therapies that address the underlying mechanical and biological dysfunctions. This knowledge is crucial for preventing the progression of tendinopathy and enhancing recovery strategies.

Towards a cellular basis of disease

The histological features of AT include disorganization of the tendon architecture, increased cellularity and vascularity. Disruption to the hierarchical Achilles tendon structure varies with the degree of injury, and ranges from microdamage during tendinopathy to complete separation and distortion after tendon rupture. The mechanosensitive and mechanotransductive aspects discussed above interact with alarmins and other damage-associated molecular patterns (DAMPs) to trigger the recruitment of $CD45^+$ cells (that is, lymphocytes, monocytes or granulocytes) to damaged tissues during the early phase of the disease[88].

Within the context of overuse-related matrix damage and failed healing response, the importance and role of inflammation in disease of these energy-storing tendons are highly debated. However, current evidence supports the role of inflammatory mediators in the onset and progression of AT[89,90] (Table 2). The precise biological mechanisms regulating the resolution of inflammation versus persistence of inflammation in AT are poorly understood, although evidence suggests that protective resolution processes become dysregulated[91], favouring the development of chronic inflammation and fibrotic repair.

Major cell types implicated in Achilles tendinopathy. Multiple cell types have been identified in tissue samples collected from patients with AT and Achilles tendon rupture[17]. ECM-producing tenocytes are the most abundant cell population found in the tendon followed by subpopulations of multipotent TSPCs[92,93] and other tendon-resident cells such as $CD45^+$ immune cells, including macrophages and T cells, endothelial cells and mural cells (pericyte subpopulations)[16–18]. Ruptures to the Achilles tendon midportion show a further increased vascularity compared with AT, probably reflecting a healing response to mechanical damage[94] with increased cellularity and cellular heterogeneity.

Tenocytes in injured tendons exhibit morphological changes, showing a rounded and proliferative phenotype, reflecting the increased metabolic and synthetic activity of these cells. Similar to

Table 2 | Inflammatory mediators described in Achilles tendinopathy

Pathway	Associated molecules	Inflammatory response	Refs.[a]
DAMPs	TLR4, S100 series alarmins, IL-33, HMGB1	Injury or tissue damage sensing and activation of pro-inflammatory signalling	82,85,91,94, 208,209
NF-κB	IL-1β, STAT6, pSTAT1	Key regulator of pro-inflammatory processes; enables protracted myofibroblast survival and promotes fibrotic progression	91,94,210
p38 MAPK	IL-6, IL-8	Promoting the production of inflammatory factors by monocytes and macrophages	91,94,211
Prostaglandin	COX2, PGE2, PTGIS	Prostaglandin production and inflammation in the Achilles tendon	94,212
Mechanical stimulation or overload	ERK1/2, PI3K, AKT, Smad2/3/4, BMP, TGFβ	Tissue repair and fibrosis	213–215
Fibroblast activation	PDPN, CD248, FAPα, CD90 (THY1)	Promote the retention of immune cells, regulating their behaviour and release of pro-inflammatory cytokines, chemokines, prostanoids and extracellular matrix proteins	91,94,95,216
Metabolic stress, oxidative stress	HIF-1α, ROS, SOD	Promote VEGF and MMP expression and mitochondrial dysfunction	88,217

AKT, protein kinase B; BMP, bone morphogenetic protein; COX2, cyclooxygenase 2; DAMP, damage-associated molecular pattern; ERK, extracellular signal-regulated kinase; FAPα, fibroblast activation protein-α; HIF-1α, hypoxia inducible factor-α; HMGB1, high mobility group box 1; MAPK, mitogen-activated protein kinase; MMP, matrix metalloproteinase; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells; PDPN, podoplanin; PGE2, prostaglandin E2; PI3K, phosphoinositide 3-kinase; pSTAT1, phosphorylated STAT1; PTGIS, prostaglandin I2 synthase; ROS, reactive oxygen species; S100, calcium binding proteins; SOD, superoxide dismutase; STAT6, signal transducer and activator of transcription 6; TGFβ, transforming growth factor-β; THY1, thymocyte differentiation antigen 1; TLR4, Toll-like receptor 4; VEGF, vascular endothelial growth factor. [a]References cite studies of well-phenotyped patient tissues, patient-derived cells or animal disease models of Achilles tendon and entheseal pathology; refs. 85,209,210,213–216 are studies in which data were obtained from animals; all other cited studies investigated human tissue.

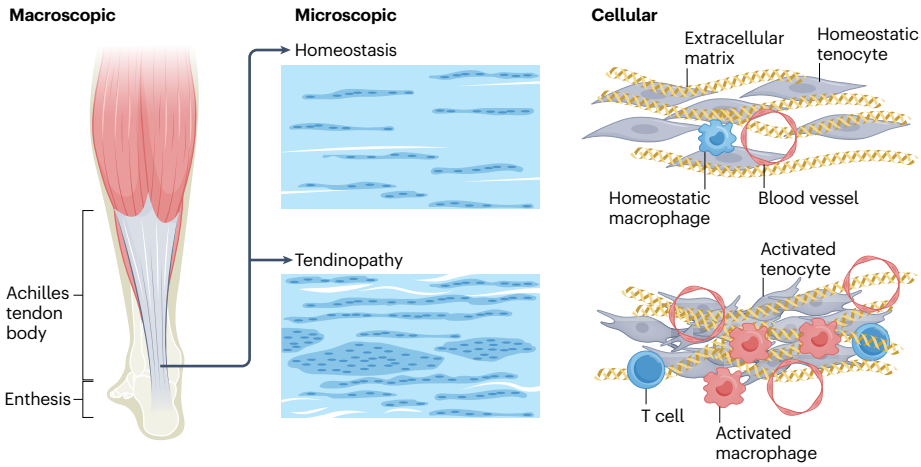

Fig. 3 | Pathological changes identified in diseased Achilles tendon and entheseal tissues. Under homeostatic conditions, the Achilles tendon exhibits highly ordered collagen fibres and the predominant cell types are tendon fibroblasts (tenocytes). During injury, the tissue exhibits increased cellularity and disrupted fibre alignment. At the cellular level, tissue-resident stromal cells including fibroblasts and macrophages exhibit an activated phenotype, accompanied by increased formation of blood vessels, immune cell infiltration and disorganized extracellular matrix due to fibrotic repair.

positional supraspinatus tendons, injured Achilles tendons express markers of fibroblast activation including THY1, PDPN, CD248, FAP and CD106 (refs. 94,95). These cells regulate fibroblast–immune cell crosstalk and have been shown to promote the retention of immune cells, regulating their behaviour and the release of pro-inflammatory cytokines, chemokines, prostanoids and ECM proteins. Advances in single-cell RNA sequencing technologies have shown that tenocytes from patient and murine Achilles tendon tissues are heterogeneous, comprising distinct fibroblast-like subpopulations[17]. Efforts to spatially resolve these fibroblasts within the context of the Achilles microstructure have identified PRG4$^+$ cells localized to the interfascicular matrix; αSMA$^+$ fibroblasts reside in the collagen-rich fascicular matrix regions during tendon repair and remodelling[69,96]. Further research is required to elucidate the biological roles of distinct fibroblast subpopulations during the development of AT, and repair and remodelling.

The increased cellularity of injured Achilles tendons is also attributable to the infiltration of CD45$^+$ immune cells to the injured site. Monocytes and tissue-resident macrophages have been identified in tissue samples from patients with AT and in patients with a ruptured Achilles tendon. Macrophages express markers of NF-κB, interferon, STAT6 and glucocorticoid receptor activation[94], suggesting a diverse range of activation states that vary with disease stage. Immune cells in pathological Achilles tendon samples from patients include CD4$^+$ and CD8$^+$ T cell populations which aid in tissue remodelling and clearance of dead and senescent cells, respectively[97]. Vascular associated cell types including endothelial cells and mural cells are abundant in injured Achilles tendons compared with healthy tissue, and reside in the interfascicular matrix and endotenon regions[16,17,94].

Tendinopathy, in general, is associated with compositional changes to the ECM, including increased levels of type III collagen mRNA and protein[98], cellular derived fibronectin and its fragments[99], and tenascin-C[100], increased glycosaminoglycan deposition at the enthesis and midportion[101], and other ECM constituents characteristic of active wound healing. Analysis of human Achilles tendons identified distinct alterations in the expression of ECM proteins and histological features between intact, tendinopathic and ruptured (acute and chronic) tendons[82] (Fig. 3). One study showed that the matricellular-protein, SPARC, is critically involved in the mechanobiology of tendons and is required for load-induced tissue maturation, homeostasis and enthesis development[81].

Modelling Achilles tendinopathy

Models facilitate the study of pathophysiological mechanisms underpinning AT. Studies range from observational studies of patient tissues, animal disease models and in vitro models. Each has its respective merits and challenges as discussed below. A combination of approaches is required to comprehensively advance our understanding of the mechanisms underlying AT.

Patient-derived Achilles tendons. Observational studies utilizing Achilles tendon tissue samples can be collected during surgical debridement or via tissue biopsy during treatment intervention[94,97]. Metadata from patient samples, including age, sex, BMI, presence of comorbidities and duration of symptoms and clinical scores, ensure that samples are well-phenotyped, such that tissue pathological changes can be interpreted relative to patient information. The challenges associated with repeated sampling of patient tissues over time preclude longitudinal studies using patient tissues to study AT and rupture. Another limitation is that samples are often obtained from patients with severe pathologies and healthy controls are difficult to include. Microdialysis might be a another method to obtain information from human and animal tissue[102].

Animal models of Achilles tendinopathy. Mice, rats and rabbits are commonly utilized to study Achilles tendon development and pathology. Models of exercise overuse, and chemical or surgical induction of injury, are frequently used in adult animal disease models, permitting longitudinal studies relative to sham controls[103]. Studies can be designed to assign function and inform disease mechanism, for example, using genetic deletion[81,104] or lineage tracing approaches[105]. Small animal models of Achilles injury frequently heal without persistent fibrosis, which is a feature of equivalent human disease; however, treadmill and other rodent overuse models can model certain features of human tendinopathy[106].

The equine superficial digital flexor tendon is a highly adapted energy storing tendon, functionally analogous to human Achilles tendon. The equine superficial digital flexor tendon operates close to its functional limits and is therefore also highly injury-prone[107]. As such, the equine superficial digital flexor tendon possesses translational relevance to human Achilles tendon injury, as similar epidemiological factors, including naturally occurring disease, effects of

ageing and high frequency of re-injury, are shared between horses and humans[67]. The interfascicular matrix region of the equine superficial digital flexor tendon plays a key role in energy-storing tendon mechanics and ageing alterations to this region negatively impact tendon function[108].

In vitro model systems. Two-dimensional models utilizing pathological stiffness or alignment can trigger certain biophysically regulated aspects of human tendinopathy, including aberrant ECM transcription[76,109]. 3D constructs can be used to model musculoskeletal tissues, facilitating functional studies of cell–cell and cell–matrix crosstalk in vitro[110]. 3D models can be tweaked to model healthy states or diseased states and constructed from animal cells or patient-derived cells[111]. One study used murine tendon assembloids to model AT, incorporating tenocytes, macrophages and endothelial cells seeded in a type I collagen hydrogel surrounding a tendon fascicle[112]. These constructs can be challenged mechanically or through defined microenvironmental stimuli to investigate emerging multicellular crosstalk during disease and injury. Challenges of a truly replicative model are associated with developing bespoke models that also accurately recapitulate the tendon-to-bone interface of the Achilles enthesis. Organ cultures comprising the calcaneus, enthesis and Achilles tendon unit isolated from rats are one approach to address this challenge, and these models can also be adapted to incorporate cyclic tensile strain[113].

Diagnosis, screening and prevention

In general, the diagnosis of AT is made based on clinical findings, and pain is the cardinal symptom of AT[20,26,36,48,114,115]. From a clinical perspective, the diagnosis of insertional AT and midportion AT should be distinguished, as these are two separate entities with different treatment approaches[26,116]. The subclassification based on symptom duration (to subdivide reactive tendinopathy from chronic or degenerative tendinopathy) has shown inconsistencies in previous literature[26,117]. Hence, only the subclassification based on location was maintained in the following description. A Delphi study was performed aiming to reach an expert consensus (with a threshold of 70%) on the diagnostic criteria for both midportion AT and insertional AT. Several diagnostic criteria reached consensus (>70%), and a distinction was made between essential and additional diagnostic criteria according to the experts[118].

The essential diagnostic criteria solely include clinical features obtained during the clinical assessment of the patient (pain-provoking tests and palpation) and patient history-taking (pain location and pain related to activity)[118]. Specifically, for the diagnosis of midportion AT, the pain is usually felt 2–7 cm above the calcaneal border[26,119] (Fig. 1). Patients experience tendon pain during (sports) activity and when palpating this particular region, which can be assessed reliably[120]. Loading tests that have been suggested as pain provocation tests to confirm the diagnosis include heel raises, jumping and hopping[121]. These loading tests will typically reproduce the patient's pain in the midportion of the tendon and should be performed progressively (with or without support, double or single leg, slowly or more quickly, on flat ground or over a step) to avoid overly sensitizing the tendon[122]. For the diagnosis of insertional AT, pain during activity and palpation is localized within the first 2 cm of the attachment of the Achilles tendon on the calcaneus[26,116,120] (Fig. 1). Patients with insertional AT also experience pain when progressively loading the tendon with the previously described loading tests[118]. Surprisingly, no consensus was reached for frequently used clinical tests such as the Arc sign or the Royal London Hospital test[120] in diagnosing insertional or midportion AT. Additionally, the presence of swelling of the Achilles tendon did not meet the consensus threshold of 70%[118]. This observation conflicts with a scoping review that aimed to propose a method to diagnose AT, indicating substantial variations in the criteria used to diagnose AT[123].

Additional diagnostic criteria (not essential but also worth considering in the diagnosis of insertional AT and midportion AT) include a decrease in self-reported function, morning or arising pain, perceived stiffness, gradual pain onset and imaging[118]. Imaging (focusing on tendon swelling, echogenicity and vascularization) can be added to the clinical diagnosis if the diagnosis is uncertain, if symptoms take an unexpected course or prior to interventional treatment[26]. Although several novel techniques have been suggested (such as ultrasonography tissue characterization and shear wave elastography), conventional and commonly accessible ultrasonography methods (B-mode, power Doppler ultrasonography) remain recommended, and if necessary, MRI or plain radiography can be considered to exclude abnormalities[26,124].

When a health-care provider encounters posterior ankle pain suggestive of AT, several differential diagnoses should be considered[20,26] (Fig. 4). The location of pain may be useful for establishing the differential diagnosis; however, this is only one aspect. Other factors, such as patient history and a thorough (clinical) examination, are also imperative for an accurate diagnosis[121]. The experts in the Delphi study reached a consensus that Achilles tendon partial tear and posterior ankle impingement (or trigonum pain) are differential diagnoses worth considering when diagnosing insertional AT and midportion AT[118]. Additionally, for insertional AT, the differential diagnoses include Haglund deformity or calcaneal exostosis, subtalar joint pain, superficial or retrocalcaneal bursitis, intratendinous calcification, Sever disease and calcaneal stress reaction or fracture[118]. For midportion AT, the differential diagnoses include tendinopathy of the plantaris, tibialis posterior or flexor tendons of the toes, sural nerve neuropathy, paratendinopathy, and accessory soleus muscle symptoms[20,118]. Notably, several of the differential diagnoses can coexist with AT, such as retrocalcaneal bursitis or Haglund morphology[26]. Additionally, in most cases, AT is suggested to be caused by overuse, but AT can also be related to other (systemic) disorders, and recognizing these disorders is crucial as different causes of AT might require different treatment strategies[26]. These disorders include systemic joint disease, familial hypercholesterolaemia, endocrine or hormonal disorders, reactions to medication, Achilles tendon rupture and diabetes mellitus or metabolic syndrome, all of which can present with symptoms resembling AT and necessitate medical attention[60,118].

Clinical assessment

The assessment of patients with AT should encompass all domains of tendon health[125,126], including the use of validated objective tools for the evaluation of pain, symptom severity, disability, function of the kinetic chain, structure and psychological factors, among others. The clinician should keep in mind that a thorough assessment is the cornerstone of proper management with long-term results. An individualized, patient-centred, biopsychosocial approach is recommended for a comprehensive management of patient-specific needs.

Validated tools that can sensitively detect clinically meaningful changes should be used to objectively quantify aspects related to all

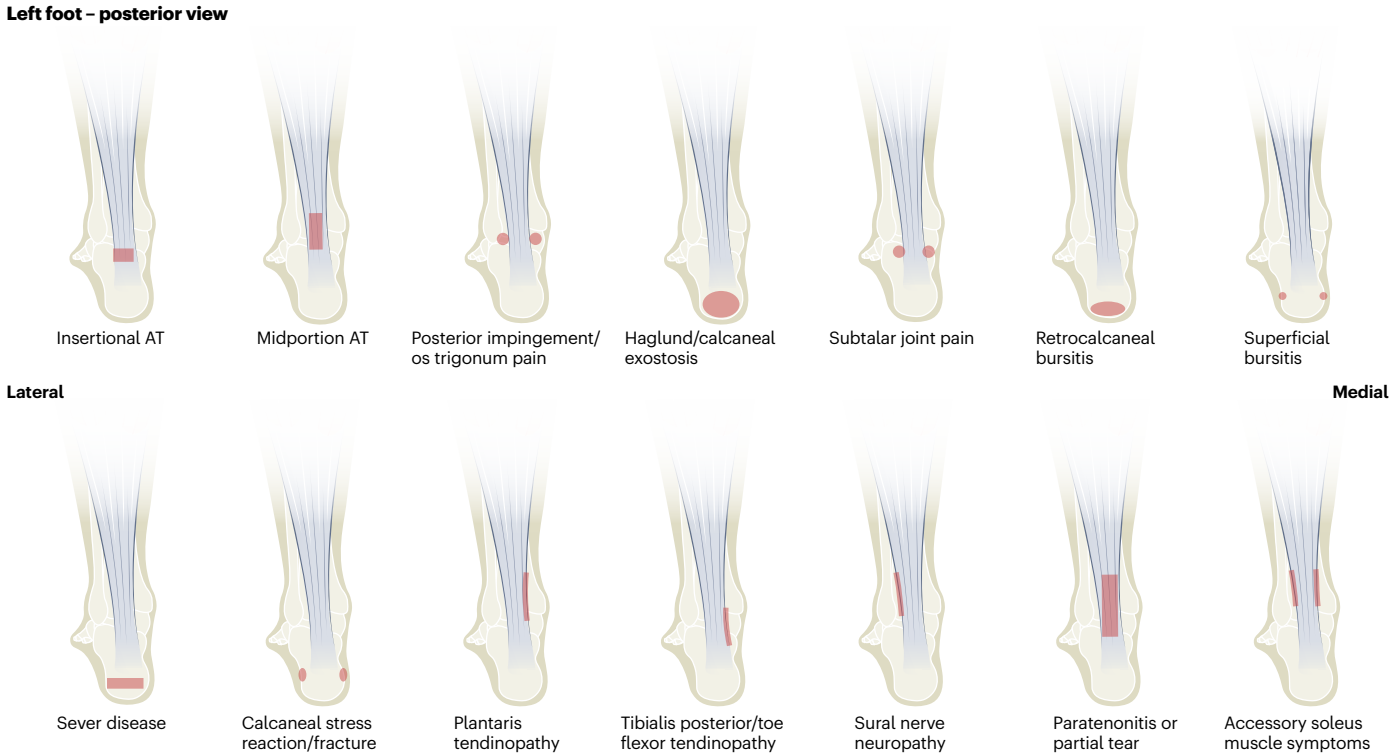

Fig. 4 | Pain location of AT and several differential diagnoses. Several conditions can mimic insertional or midportion Achilles tendinopathy (AT) by causing heel pain and need to be considered in the differential diagnosis. When evaluating posterior ankle pain suggestive of AT, clinicians should (among others) carefully analyse pain behaviour to accurately determine the underlying condition. This image depicts the typical pain locations (red marks) associated with various conditions. Note that pain locations represent patient-reported symptoms rather than areas of tenderness identified through palpation. Adapted with permission from ref. 257, Barça Innovation Hub.

core domains[122,125–128]. The pain numeric rating scale has been recommended to measure an individual's pain on palpation and pain with activities, such as heel raises and hopping[127,128]. Symptom severity and disability should be assessed using patient-reported outcome measures specific to patients with AT, such as the Victorian Institute of Sports Assessment–Achilles (VISA-A)[129], the VISA-A Sedentary[130] and the Tendinopathy Severity Assessment–Achilles (TENDINS-A)[131]. Additionally, Patient-Reported Outcomes Measurement Information System (PROMIS) is designed to measure a more broad range of health domains, including the impact of AT on mental health and quality of life[132].

Although patient-reported questionnaires for assessing physical activity in AT are of great value, they are often flawed by issues such as recall bias, floor effects, and concerns about reliability and validity[133]. The function of the ankle plantar flexors can be assessed using the standing heel-rise test[134], dynamometry[40], the seated calf raise six repetition maximum[50], as well as the single-limb jumping ability[40,122,134]. Assessment of the function of the kinetic chain muscles, including the knee extensors[50], and the hip abductors and extensors[51], using repetition maximum tests or dynamometry could also be considered in the assessment of a patient with AT.

Ultrasonography is the preferred method for imaging the Achilles tendon according to current clinical practice guidelines[26,115]. Ultrasonography can be used to assess tendon morphology (that is, cross-sectional area and/or tendon thickness) and the presence of abnormalities (bursitis, calcification or bony deformity, neovascularization, among others)[125,127].

The normal Achilles tendon should have an echogenic pattern of parallel fibrillar lines in the longitudinal plane and an echogenic round-to-ovoid shape in the transverse plane[135]. On transverse imaging, the normal Achilles tendon has a flat to concave anterior surface and measures 4–6 mm in anteroposterior diameter[135]. In one study including >600 participants, in asymptomatic individuals, the median tendon thickness was 4.9 mm (3.8–6.9 mm) for the midportion region and 3.7 mm (2.8–4.8 mm) for the insertional region[136]. In tendinopathy, focal or diffuse swelling of the Achilles tendon is most commonly seen, with tendon thickness ranging from 7 mm to 16 mm in patients who have a clinical diagnosis of AT[135]. Altered echogenicity and the presence of neovascularization (peritendinous or intratendinous) are abnormalities that may also be observed in patients with AT[26]. Furthermore, shear wave elastography and ultrasonography tissue characterization are emerging as new technologies to provide additional information about tendon mechanical properties and tissue alignment[125].

Finally, psychological factors such as kinesiophobia and pain catastrophizing should not be neglected and can be objectively measured with the Tampa Scale of Kinesiophobia[137] and the Pain Catastrophizing Scale[138]. Current evidence suggests that a thorough assessment including these different domains of tendon health may be determinant in identifying subgroups of patients with AT[139], which may be important for personalized, patient-centred management.

Prevention

Few studies have investigated the effects of interventions to prevent AT and the evidence from studies assessing effectiveness of interventions is generally low. A prospective cohort study investigated whether soccer-specific sensorimotor training could reduce the occurrence of AT in elite female soccer players[140]. The intervention involved weekly plyometric exercises (exercises involving repeated rapid eccentric and concentric contractions, optimizing movement via the stretch–shortening cycle) and balance training performed after a short warm-up[140]. The authors observed that there was a significant decrease in the incidence of AT (from 1.5 to 0.0 per 1,000 h) after the intervention. Another study found that using shock-absorbing insoles inside the boots significantly reduces the incidence of AT in military recruits[141]. Furthermore, one study investigated the effects of a 14-week preventive intervention in male soldiers[142]. Participants in the control group, who received no intervention, had an increase in echo types III and IV (disorganized collagen fibres and fibrillar matrix) and a decrease in echo type I (normal fascicular structure, with continuous and aligned collagen bundles) in the Achilles tendon evaluated via ultrasonography tissue characterization[142]. By contrast, those in the intervention group, who performed trunk and lower limb muscle balance and strengthening exercises, showed no change in the tendon echo types after 14 weeks of intense military training, potentially indicating that the intervention had a protective effect on tendon structure[142].

Achilles tendon loading exercise programmes are often used for the treatment of AT. However, care should be taken with the implementation of eccentric exercises as a preventive intervention for athletes in-season. One study found that an intervention composed of eccentric exercises and stretches not only did not have a protective effect but also caused tendinopathy in previously asymptomatic soccer athletes who had Achilles tendon abnormalities on ultrasonography at the beginning of the season[143]. This finding may indicate that a high-load intervention in athletes already submitted to the high loads of the competitive season may be excessive in not allowing enough time for the tendon to recover from the stimulus.

Management

The first line of AT management should include progressive load exercises, education and activity advice[26,28,36,115]. The goal is to empower individuals to understand their condition and its biopsychosocial contributors, to enable them to develop competencies for long-term self-management via load modification and exercise strategies[122]. For a higher chance of long-term success, the intervention needs to consider the multifactorial aetiology of AT, and take into account known risk factors, potential causes of overuse[22] and all domains of tendon health[127].

Exercise programmes

Progressive loading exercises are the cornerstone of AT management[26,28,36,115]. For decades, the heavy-load Alfredson eccentric protocol[144] (HLAE protocol) was considered the gold-standard intervention for managing AT. However, low certainty of evidence shows that the HLAE protocol is better than wait-and-see approach[145], and other exercise interventions (for example, heavy slow resistance[146] and the Silbernagel protocol[127,147]) seem to be more effective than the HLAE protocol[122,145]. Patient compliance is lower with the HLAE protocol than with the heavy slow resistance intervention[146] and participant-rated global perceived effect is lower with the HLAE protocol than with the Silbernagel protocol[148]. The fact that 60% of patients with AT treated with the HLAE protocol experience persisting symptoms[9] is reason for concern, indicating that this intervention might not be a long-term solution for the majority of patients. However, to date, no loading intervention has proven superiority over others in improving pain and function in individuals with AT. Hence, clinicians can choose among the several exercise-based programmes that have been shown to be effective for the management of AT[149]. Currently, programmes involving different exercises in progressive phases are recommended[26,122,127,150–152] (Fig. 5). This progression is relevant to gradually build load tolerance in the tendon as high-velocity exercises produce a much higher load than slow-velocity exercises[72,153].

Rehabilitation phases. In phase 1, when the tendon has low capacity and high irritability, strategies to reduce excessive Achilles tendon load are recommended. High-velocity tensile and compressive loads should be avoided initially[122,150]. Education focusing on pain neurophysiology and on AT pathophysiology reduce fear of movement and improve self-efficacy in patients with AT[150]. Patient-centred educational interventions that focus on activity modification, independent symptom management and expectation adjustment are recommended[122]. The pain monitoring model (that is, allowing sports activities with a pain score of ≤5 out of 10) is effective as a load management strategy[127,147]. However, in individuals in whom load tolerance is severely compromised, reducing volume or even ceasing sports activities during treatment may be necessary[122]. Strengthening the kinetic chain muscles (that is, quadriceps and gluteus maximus) may also be important to decrease the demand on the Achilles tendon[50,51,151]. Other strategies to decrease Achilles tendon load in the initial stage include using heel lifts[154] and increasing step-rate during running[155]. To start providing therapeutic loading to the Achilles tendon, lower-load exercises[72,153], such as double-leg and single-leg slow heel raises, may be good options. If dynamic contractions are too painful (pain score of >5 out of 10), isometric exercises (exercise involving static contraction of a muscle without any visible movement in the angle of the joint) are recommended in the initial stage[26,122].

Phase 2 involves progressive slow-velocity isotonic triceps surae exercises[26,122]. If the patient has access to a gym, exercises such as heel raises in the Smith machine, heel raises in the leg press, and heel raises in the seated calf raise machine are recommended, to be performed slowly (6 s per repetition) in three or four sets for each exercise, three times per week, progressing from a load of 15 repetition maximum (RM), to 12 RM, then 10 RM, 8 RM and finally 6 RM as recommended in the heavy slow resistance protocol[146]. If the individual does not have access to a gym, heel raises can be performed at home, initially on the ground, then using a step to increase the range of motion and optimize tendon loading, and using backpacks or other objects the individual can access at home as additional weight[122,127,147,150]. The pain monitoring model[127,147] may be used to facilitate the individual's understanding of the amount of pain allowed during and after an exercise (that is, a pain score of ≤5 out of 10), as well as to determine exercise progression[48].

In the advanced stage of managing athletes with AT, plyometric exercises and sport-specific exercises will gradually be introduced into the rehabilitation[122,127,147,150,151,153], which is particularly relevant as individuals with AT display deficits in power[40], and these deficits need high-velocity exercises to be reversed[156].Progression to phase 3 can be made when the individual has a pain score of ≤3 out of 10 24 h after phase 2 exercises and has reached the minimum strength to withstand high-velocity exercises. The desirable minimum strength to be achieved is 1.5 times body mass 6 RM in seated calf raise and 0.5 times body mass 6 RM in standing calf raise prior to starting phase 3

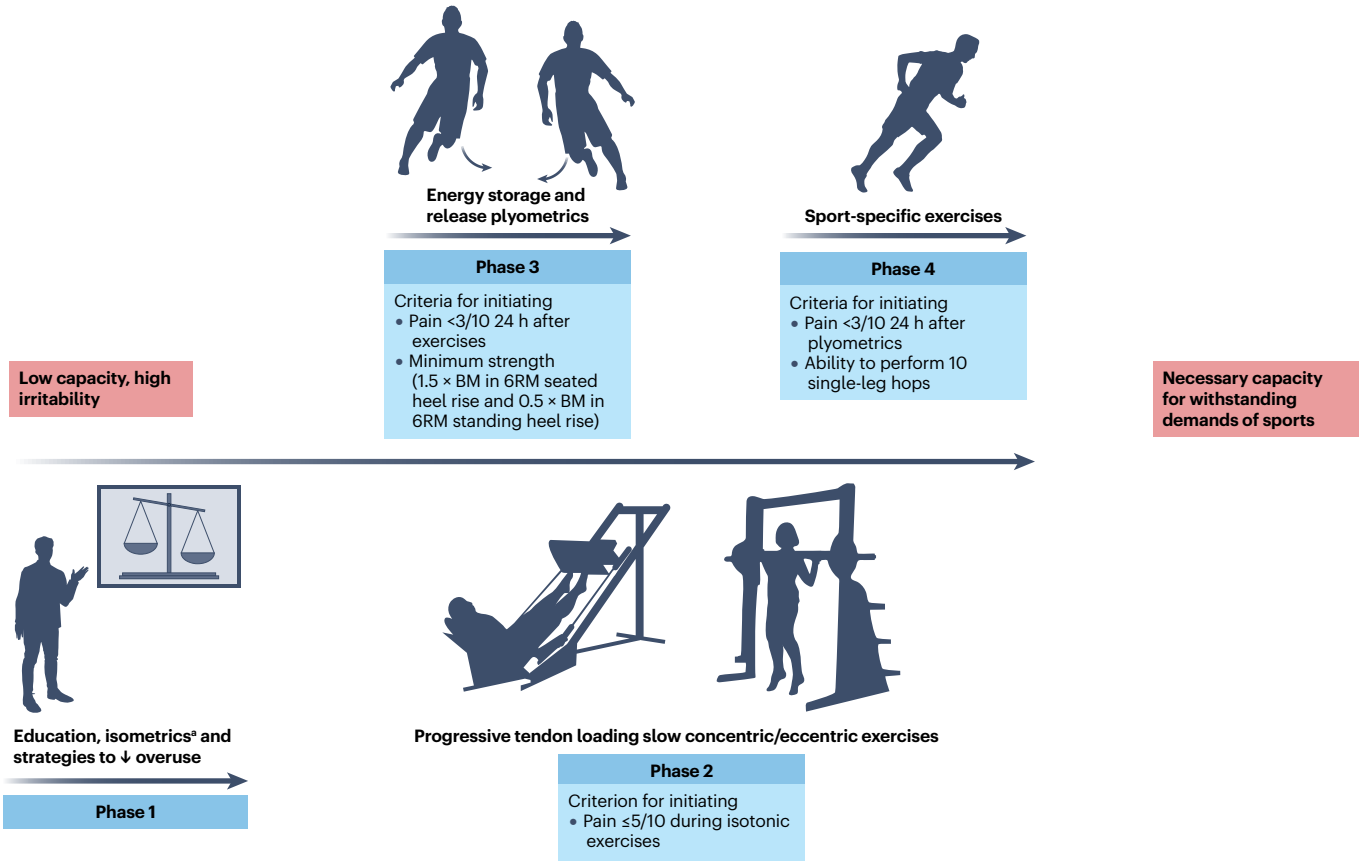

Fig. 5 | First line of management in stages of an athlete with Achilles tendinopathy. Phase 1 involves education focusing on pain science or neurophysiology of pain and on load management, strategies to reduce excessive Achilles tendon load (that is, strengthening the gluteus maximus and quadriceps, heel lifts, among others), and triceps surae isometric exercises (if isotonic exercises are too painful). Phase 2 involves slow concentric and eccentric triceps surae exercises with progressive load, both with the knee straight (focus on the gastrocnemius) and the knee bent (focus on the soleus), initially in double-limb progressing to single-limb. In phase 3, high-velocity energy storage and release exercises such as plyometrics are gradually introduced. Phase 4 involves explosive sport-specific exercises, such as running, jumping and changing direction. Criteria for progressing between stages consider pain during the exercises as well as 24 h after the exercises (assessed on a 0–10 numerical pain rating scale) and milestones of functional capacity (minimum strength, ability to hop without experiencing a flare-up in symptoms, among others). A gradual progression is important to reduce the frequency of flare-ups and to prevent recurrences. A biopsychosocial approach involving multiple professionals is important to contemplate the multifactorial aetiology of Achilles tendinopathy and encompass all domains of tendon health. BM, body mass (kg); RM, repetition maximum. [a]Only if concentric or eccentric exercises are too painful (pain score >5/10).

submaximal hopping exercises[50,122]. Phase 3 plyometric exercises include multiple variations of double-leg and single-leg jumps and landings[72,150,151,153]. The recommended frequency of plyometric exercises is three times per week[150,151]. At least two days of rest between sessions is recommended[147] so that the tendon has sufficient time to undergo ECM turnover, which requires at least 36 h of rest between high-load exercises or activities[157]. Phase 2 exercises should be continued three times per week until the individual reaches a load of 6 RM, which typically takes 12 weeks. After that, it is recommended that phase 2 exercises are performed once or twice per week to continue improving load tolerance[122]. In advanced stages, phase 2 exercises may also progress from double-limb to single-limb. Phase 4 exercises include, for example, jogging, interval running at a slow pace, progressing to sprinting, deceleration and change of direction[127,147,150–152], according to athlete-specific need until the demands of full return to sport are achieved. Return to sport criteria should be followed to reduce the risk of recurrence[158].

Although the duration of AT typically lasts between 3 months and 1 year, only one-third of athletes with AT return to pain-free sports, and up to 20% with midportion AT still have symptoms up to 10 years after the initial presentation of tendinopathy[159]. Even if a athlete recovers symptom-free, the risk for re-occurrence is large. Among runners with AT, the most frequent reason for developing AT is the presence of previous symptoms within the last 12 months[35].

Insertional AT needs to be managed taking into consideration that compression of the tendon insertion against the calcaneus, such as that which occurs in calf stretching or activities with high dorsiflexion range, is considered one of the causes of insertional AT. In the initial stages, heel lifts to keep the ankle in plantar flexion are recommended to minimize tendon compression against the calcaneus[160]. Other compression-causing activities to be avoided include stretching and uphill running. Avoiding dorsiflexion during rehabilitation exercises has also been recommended[26], as a low success rate with full range of motion has been reported[161]. Gradual

reintroduction of dorsiflexion should be performed at advanced stages guided by pain[122].

Secondary tendinopathy

Secondary tendinopathy (as a consequence of another health condition)[162] also needs to be managed taking into consideration the factors contributing to AT pathophysiology. Common comorbidities of secondary tendinopathy include diabetes mellitus, which is associated with more severe tendon degeneration than non-diabetic tendinopathy[163], and high cholesterol, which can accumulate in tendons and lead to tendon xanthoma in extreme cases[164]. Other health conditions that have been associated with tendinopathy include obesity, hypertension, hypercalcaemia, dyslipidaemias, haemochromatosis, endocrinopathies (such as thyroid disease, Cushing syndrome, hypogonadism and menopause), rheumatoid disease, gout, pseudogout, heritable connective tissue diseases, psoriasis, and spondyloarthropathies, among others[47]. Holistic assessment of AT should include the assessment and treatment of the underlying conditions that contribute to the pathophysiology of tendon pain. For example, the treatment of a patient with AT secondary to diabetes mellitus would probably benefit from interventions such as daily exercise to promote glycaemic control (decreasing the deleterious effects of advanced glycation end-products on tendon health), aerobic training and resistance training with more slowly and carefully progressed loads than in patients without diabetes mellitus, owing to the deleterious effects of diabetes mellitus on tendon function[162].

Adjuncts to exercise

Adjunct treatments are an often-used, and much debated, component of AT treatment. In a survey of patients with midportion AT, 94% reported being prescribed exercise, and 46% also received adjunct treatments, of which the most common (27%) was injections (such as corticosteroid and platelet rich plasma)[165]. Clinical practice guidelines[26,115] suggest that if exercise and education are not sufficiently effective, adjuncts may be considered through shared clinical decision-making with the patient (Table 3). The patient populations represented in existing literature are typically small (<100) and vary substantially in age, build (athletic versus non-athletic), sex and symptom acuity, so caution must be applied when generalizing from these findings. The proposed mechanisms of action vary, reflecting uncertainty about the underlying causes of AT. In some instances, the proposed mechanisms of action suggest diametrically opposed goals (for example, resolution of inflammation, or induction of inflammation to initiate a healing response). Further research is required to establish a firm role for adjunct therapies.

Surgical intervention

Surgical treatment is considered when conservative approaches, including adjunct therapies, have failed to provide relief. Typically, surgical intervention is only recommended after unsuccessful conservative management[29]. However, the lack of robust, high-quality, comparative studies evaluating the optimal surgical strategy for the management of AT underscores the need for caution when considering invasive procedures, particularly given the associated complication rates. Surgical intervention should not be viewed as a guaranteed solution but as a crucial strategy when all other treatments have failed.

Midportion AT. Traditionally, open surgical techniques for midportion AT entail an extensive incision with the patient positioned prone followed by excision of the pathological tissue[166]. In cases of severe tendinopathy with poor quality remnant tissue, an autologous tendon transfer is indicated[166]. Typically, the flexor hallucis longus tendon is utilized owing to its favourable biomechanical properties[167]. Return to sporting activities is facilitated at 3–6 months postoperatively[30]. However, variable success rates with high complication rates have been reported following surgery. In one study, the complication rate in a cohort of 432 patients was 11% following open Achilles surgery[168]. The poor vascularity of the local soft tissue envelope predisposes patients to wound infection, seroma formation, haematoma formation and thromboembolic events. Additionally, the proximity of the sural nerve that runs adjacent to the lateral border of the Achilles tendon can result in inadvertent iatrogenic injury during the surgical approach.

To circumvent the high complication rates associated with traditional open surgical debridement of the Achilles tendon, minimally invasive Achilles tendoscopy has been developed[169]. Achilles tendoscopy involves the use of an incision of 2–4 mm at two separate portal sites followed by insertion of a 4.0 mm endoscope into the tendon sheath. The endoscope and associated surgical instruments, such as a shaver and Freer elevator, are used to visualize the Achilles tendon, debride any degenerative changes, resect any adherent plantaris and release adhesions surrounding the tendon (Fig. 6). Additionally, a spinal needle is utilized to create microperforations in the tendon to stimulate neovascularization (Fig. 6). Once the procedure is complete, a biological adjuvant such as platelet-rich plasma can be administered to the site by percutaneous injection. However, evidence supporting its efficacy remains inconclusive (see Table 3). In addition to the treatment of the diseased portion of the tendon, Achilles tendoscopy also allows any pathological changes in the mid-substance of the tendon that was not identified on preoperative assessments and imaging to be addressed. Postoperative management of minimally invasive procedures involves full weight bearing after 1–2 weeks, with return to sports activities typically after 6–12 weeks[30].

A retrospective study demonstrated excellent results in patients undergoing Achilles tendoscopy for the management of chronic midportion AT with a median follow-up of 87 months[170]. Ten of the 11 patients were satisfied, achieving full pain relief at rest within a median of 9 weeks and returning to their preoperative sporting levels at a median time of 4 months. The median postoperative VISA-A score at the final follow-up was 100, indicating excellent functional recovery. The safety of the procedure was underscored by a 0% complication rate and a 0% reoperation rate. Furthermore, a retrospective review evaluated 45 patients who underwent Achilles tendoscopy for the treatment of midportion AT with a median follow-up time of 67 months for unilaterally treated patients and 89.5 months for bilaterally treated patients[171]. Patient satisfaction was high, with median scores of 9 out of 10 for unilaterally treated patients and 9.5 out of 10 for bilaterally treated patients, and 83% indicated that they would undergo a repeat procedure. Functional outcomes remained excellent at mid-term, with median VISA-A scores of 81 observed in the unilateral cohort and 97 observed in the bilateral cohort, and pain scores during running and sports reduced to a median of 1 or 0. Only one patient required reoperation[171]. Although these findings are encouraging and highlight the durability and effectiveness of this endoscopic approach in providing sustained relief and promoting functional recovery, the limited quality of evidence and small patient cohorts underscore the need for further research to confirm these results in larger and more diverse patient populations.

Table 3 | Adjunct treatments investigated in placebo-controlled randomized controlled trials for AT

Proposed intervention	Proposed mechanisms of action	Possible side effects	Best evidence	Refs.
Electromodalities				
Focused shockwave	Destruction of calcifications, pain relief and tissue repair	Temporary pain, bruising, tendon rupture in older patients	Small placebo-controlled RCT, no significant difference in pain outcomes between intervention and control groups	218
Radial shockwave	Tissue repair	Temporary pain, bruising	RCT in 48 participants, radial shockwave, when combined with progressive loading exercises, may improve pain and function in the short term For insertional AT, however, no added benefit was found	219–221
Laser therapy	Reduce inflammation, tissue repair	Damage to the eye or skin	Study quality and results between trials are inconsistent, precluding firm conclusions about efficacy	222–226
Injections				
PRP	Tissue repair	Increased tendon pain and inflammation	Four of five placebo-controlled RCTs concluded that PRP provides no clinical benefit	227–231
High-volume saline	Disrupt neovessels and adhesions	Pain, inflammation, tendon rupture	Study quality and results between trials are inconsistent, precluding firm conclusions about efficacy	152,228
Polidocanol	Disrupt neovessels or nerves	Injection site pain, irritation, pruritus	Study quality and results between trials are inconsistent, precluding firm conclusions about efficacy	232,233
Ultrasound-guided corticosteroid	Reduce tendinopathic cellular activity	Injection pain, recurrence or worsening of symptoms	RCT in 100 participants, ultrasound-guided corticosteroid injection (placed peritendinous anterior to the tendon in the Kager triangle), when combined with structured rehabilitation and activity restrictions, may improve pain and function in the short and long term	234,235
Topical treatment				
Topical GTN ointment	Enhance tendon healing	Headaches and local rash	RCT in 65 participants found that GTN in addition to exercise rehabilitation was superior to placebo for pain reduction at 12 and 24 weeks in patients with AT However, another RCT in 76 patients with AT with symptoms for >3 months who were also treated with exercise, found no difference in outcomes between GTN and placebo over 24 weeks	236,237
Oral NSAIDs				
Naproxen	Reduce inflammation	Gastrointestinal erosions, renal or hepatic insufficiency	RCT in 69 participants with symptoms for <3 months who were engaging in rehabilitation found no added benefit of naproxen over placebo	238
Piroxicam	Reduce inflammation	Gastrointestinal erosions	RCT in 70 participants who were engaging in rest followed by rehabilitation found no added benefit of piroxicam over placebo	239

AT, Achilles tendinopathy; GTN, glyceryl trinitrate; PRP, platelet-rich plasma; RCT, randomized controlled trial.

Achilles in-office needle tendoscopy (IONT) is an emerging surgical strategy that is performed with the patient wide awake in the office setting using a 1.9 mm endoscope without the use of a tourniquet[172,173] (Fig. 6). The use of a 1.9 mm endoscope minimizes trauma to the soft tissue envelope, substantially reducing the risk of wound complications. Additionally, it eliminates the need for general anaesthesia, thereby reducing associated risks, and enables immediate weight-bearing after the procedure, enhancing patient recovery. Postoperative management of Achilles IONT involves immediate range of motion exercises and weight bearing in regular shoe wear to prevent the formation of cicatrized scar tissue, potentially leading to accelerated return to activity compared with traditional open Achilles debridement and endoscopic Achilles tendoscopy with the use of a 4.0 mm endoscope. A retrospective case series evaluated 12 patients who underwent Achilles IONT for the treatment of midportion AT with a mean follow-up time of 26.3 months[172]. Most patients (91.7%) achieved a minimum clinically important difference as evaluated by both the VISA-A and a visual analogue score (VAS), and patient satisfaction was high. Most patients returned to work within 4.2 days and sporting activities within 5.9 weeks. Overall, a low complication rate was observed, including one patient with sural neurapraxia and one with persistent pain requiring repeat IONT. These promising early results suggest that IONT is a potential next-generation treatment for chronic AT, with notable clinical improvements and high patient satisfaction. However, validation through larger prospective studies is needed, as current findings are based on a single small retrospective case series.

Insertional AT. Various surgical techniques are employed to manage insertional AT, including both endoscopic and open techniques. In the setting of Haglund deformity, a multicentre prospective study showed that endoscopic calcaneoplasty is an effective surgical strategy with faster recovery, but demonstrated 1-year results similar to those of open surgery[174]. In addition to the treatment of the diseased portion of the tendon, Achilles tendoscopy also allows any pathological changes in the mid-substance of the tendon that was not identified on preoperative assessments and imaging to be addressed. Following open

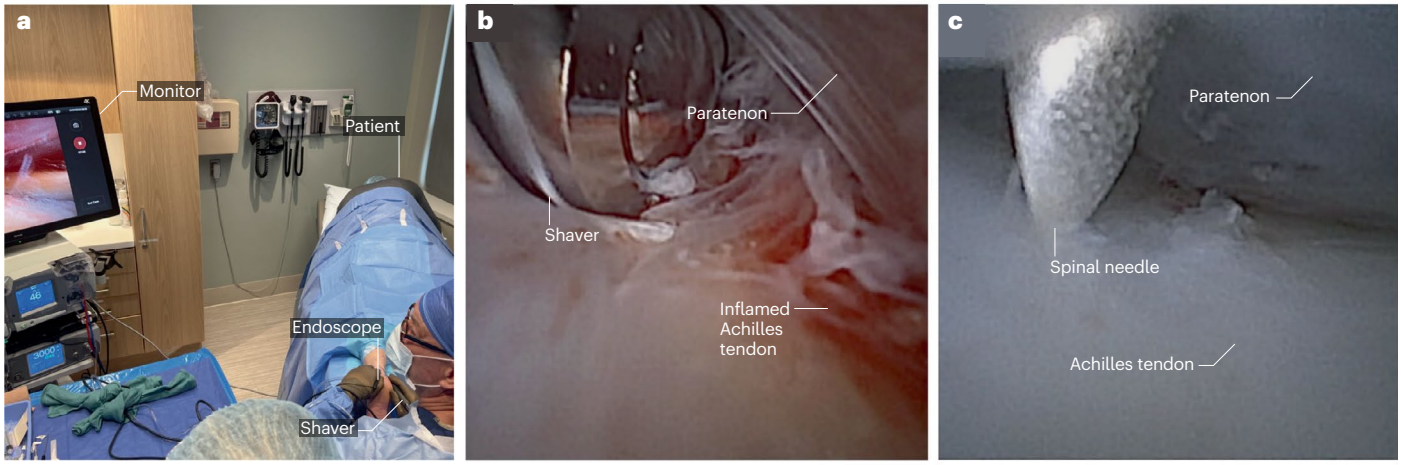

Fig. 6 | Minimally invasive in-office needle Achilles tendoscopy. a, In-office needle Achilles tendoscopy of the left Achilles tendon. **b**, Shaver debriding degenerative changes of the right Achilles tendon. **c**, Endoscopic view of the right Achilles tendon demonstrating a spinal needle creating microperforations in the substance of the tendon to stimulate neovascularization.

debridement and excision of the pathological tendon, reattachment is typically achieved using a single-row or double-row suture repair. Both approaches aim to enhance the footprint — the area where the tendon is fixed to the bone — thereby optimizing conditions for tendon healing. A meta-analysis comparing single-row versus double-row suture for the management of insertional AT showed similar clinical outcomes with both techniques, although preclinical biomechanical studies showed superiority of the double-row suture[175]. Numerous osteotomies, such as a Zadek osteotomy, have been described for addressing a large Haglund deformity, but are associated with a protracted recovery period and higher complication rates, particularly with respect to symptomatic hardware and non-union compared with calcaneoplasty[176].

In summary, although surgical intervention remains a valuable option for AT when conservative measures fail, the limited high-quality evidence supporting its efficacy highlights the need for cautious consideration[177,178]. Further large-scale randomized controlled trials are needed to establish these procedures as reliable standards of care and optimize surgical treatment strategies for AT.

Quality of life

Quality of life may be defined as "the degree of excellence in life (or living) relative to some expressed or implied standard of comparison…" and includes "aspects that make life particularly enjoyable, happy and worthwhile, such as meaningful work, self-realization (as in the full development of talents and capabilities), and a decent standard of living."[179]. Individuals with AT have reduced quality of life as a consequence of different aspects of their condition. Pain[180], limited physical activity levels[181], reduced level of sport or work performance[182], reduced social participation[183], reduced enjoyment of life[184] and even depression and anxiety[185] can occur in patients with AT.

A systematic review involving 2,070 individuals with AT comprising men and women equally reported a lower quality of life in patients with AT than in those without AT, and the effect size was considered substantial[186]. Indeed, the quality of life was similar or worse than in populations with arthritis (rheumatoid arthritis or osteoarthritis). Quality of life was found to be reduced in sedentary individuals and those active in sports, but the reduction was stronger in those involved in sports[186]. The instruments used to measure quality of life in these studies included the 12-Item short form survey (SF)-12, the 16-Item SF-16, Assessment of Quality of Life 8 dimensions (AQOL)-8D and EQ-5D.

The systematic review mentioned a UK study including 320 patients with AT (125 male, 195 female), the majority of whom had insertional tendinopathy. Quality of life was significantly lower in those with AT who were <55 years of age[187]. No difference in quality of life was observed between those with midportion AT versus insertional AT.

An exploratory Australian study in 92 men and women with AT used the AQOL-8D combined with focus groups and interviews to explore the influence of patient experience on quality of life[188]. On average, quality of life in patients with AT was lower than normative values of the general population, and this impact involved both mental and physical health, and pain and/or sensory aspects. In this study, a conceptual model was presented whereby the impact of AT on quality of life is worse in situations where there is increased lifestyle impact, presence of a comorbidity (for example, asthma, depression or arthritis), a poor response to treatment, or confusion about the condition (for example, uncertainty about best treatment or questioning the ability to recover). On the other hand, positive beliefs (feeling in control or confident of improvement), minimal lifestyle impact (for example, ability to find alternative activities), good response to treatment, and good self-management resulting from coping and knowledge, were suggested to reduce the effect of AT on quality of life[188].

Importantly, AT can have substantial economic impact, which may influence quality of life. In a Dutch cross-sectional survey in 80 patients with AT, 38% reported an impact on their productivity at work, with an estimated cost of US $991 per patient and an average of nine annual health-care visits[180]. Inquiring about patient experience of chronic Achilles tendon pain or discomfort and the associated effects on quality of life may be helpful in developing individualized therapeutic relationships and rehabilitation plans. For example, coaching on adapting or switching physical activities, providing knowledge about the condition, developing coping strategies, such as access to exercise space, time and equipment, addressing potential negative beliefs

about the potential for recovery (such as kinesiophobia) or perceived ineffectiveness of exercise, may be beneficial in minimizing the effect of AT on quality of life[165].

Prognosis

The prognosis of AT is variable, with some patients showing resolution in a few weeks[189], others showing improvement in months to years, and many failing to show full resolution. Symptom duration, however, is unrelated to the severity of symptoms or course of recovery with conservative exercise-based treatment[117]. A prospective cohort study found that one-fifth of patients had ongoing symptoms 10 years after receiving treatment[159]. In that study, only 37% of active patients had resumed sports at their pre-injury level, indicating potential long-term impacts on quality of life. A living systematic review showed that most patients with midportion or insertional AT undergoing an active treatment of any kind will experience some improvement between 3 and 12 months, and that any kind of active treatment provides superior results to a wait-and-see approach; however, the systematic review noted that 76% of trials included were at high risk of bias[28]. In 664 patients with insertional AT, four factors (higher pain, lower ankle range of motion, prior corticosteroid injection and presence of enthesophytes) were associated with worse outcomes – if all four factors were present, the success of conservative treatment was only 45%[190].

Outlook

Although it is widely accepted that controlled exercise-based programmes are effective as the first-line management of AT, no consensus is available on optimal adjunct therapies owing to the highly heterogeneous clinical outcomes observed across studies and patient populations (see also Table 4). The lack of consensus highlights the urgent need for improved evidence-based adjunct treatments and the investigation of innovative therapies, underpinned by high-quality studies assessing their efficacy (Box 2). Ongoing basic research aims to identify the key cell types and ECM molecules implicated in the development and progression of AT, to further deepen our understanding of the cellular basis of disease. Access to well-phenotyped patient tissues and the development of refined model systems will collectively advance our knowledge of how local tissue biomechanics influences pathological processes during Achilles pathology, repair and rehabilitation. These advances and transdisciplinary efforts will inform the development of new therapeutic strategies to precisely target pathogenic cell types and ECM molecules implicated in AT.

Clinical trials

In addition to ongoing clinical trials investigating various exercise and loading regimens aiming to provide more robust data and enhance the effectiveness of these interventions (Table 4), advances have been

Table 4 | Selected ongoing interventional clinical trials for AT therapies in 2025

Intervention (study number)	Proposed mechanism of action	Disease	Refs.
Dietary supplementation			
ω3-Rich food (ACTRN12622000980730)	Modulate inflammation	AT	240
Retinyl palmitate (SLCTR/2023/016)	Inhibit scar formation	AT	241
Pharmacological			
NGI226 microparticles (NCT05592990)	Inhibit activation of Janus kinases; modulate inflammation	Midportion AT	242
Metformin (NCT06100822)	Modulate inflammation	Midportion AT	243
Topical glyceryl trinitrate with phonophoresis (NCT05561959)	Enhance tendon healing	Midportion AT	244
Biomaterials and regenerative medicine			
AmnioFix (human amniotic membrane matrix) (NCT06172218)	Replacement or supplement damaged tissue; modulate inflammation or tissue lubrification	Chronic insertional or midportion AT	245
Collagen-based medical device (NCT05464498)	Replacement or supplement damaged tissue or tissue lubrification	AT	246
Extracorporeal shockwave therapy combined with platelet-rich plasma (NCT06384859)	Combination of mechanical and biological stimulation	Insertional AT	247
Rehabilitation, exercise and surgery			
Percutaneous electrolysis (NCT05301959, NCT03167554)	Generation of a local inflammatory response; analgesia	AT	248,249
Pulsed electromagnetic field (NCT05316961)	Reduce pain, tissue repair	AT	250
Reinsertion Achilles tendon vs Zadek osteotomy (NCT06322381)	Decrease stress across the tendon at its insertion (Zadek osteotomy)	Insertional AT	251
Proximal medial gastrocnemius recession (NCT05179551)	Relieve tension in the Achilles–calcaneus–plantar system	Midportion AT	252
Isometric exercise programme with biofeedback and dose monitoring (ISRCTN57756415)	Restore mechanical and morphological properties of tendons	AT	253
Exercises with different intensities (RBR-4vwy5xj)	Restore mechanical and morphological properties	AT	254
Heel lift inserts (ACTRN12623000721606)	Reduce tendon load	AT	255
Dry needling (NCT03968614)	Local bleeding, cell proliferation and differentiation	AT	256

AT, Achilles tendinopathy.

made in the clinical development and use of different novel therapies for tendon diseases[191]. Nonetheless, a serious limitation in the field is that the majority of therapies are either tendon-unspecific or have only been tested in other tendons, overlooking the specific characteristics of the Achilles tendon in health and disease. Although potential treatments for tendinopathies have been suggested to encompass novel pharmacological, regenerative medicine and nanotechnology strategies (reviewed elsewhere[48,191]), only a limited number of studies have shown beneficial clinical effects as adjunct therapies in AT (Table 3). Currently, a few novel treatments are being clinically tested for AT; these include biomaterials (such as amniotic membrane or injectable medical devices based on collagen) used as temporary scaffolds for tendon-resident cells or implanted cells, which have been hypothesized to reduce pain and improve function in damaged tendons. Furthermore, some biomaterials, such as AmnioFix, have been suggested to modulate inflammation and to provide tendon protection by lubrification[192]. In addition, repurposing approved drugs, such as metformin, a medication used to treat type 2 diabetes mellitus with anti-inflammatory and immunomodulatory properties[193], is gaining much research attention owing to its cost-effectiveness. Finally, various dietary supplementation strategies are under investigation for their potential in treating AT (Table 4).

Tissue engineering and regenerative medicine

The development of new therapeutics for AT treatment will need to integrate knowledge and strategies that promote Achilles tendon tissue regeneration, mimicking tendon tissue architecture and biomechanical behaviour, and modulating the immune response for proper inflammation resolution. These novel therapies will potentially rely on advances in tissue engineering and regenerative medicine, combining drugs, biologics and biomaterials for synergistic effects. Notably, combining biomaterials with repurposed drugs, such as the immune modulator rapamycin with polylactic-co-glycolic acid (PLGA) nanoparticles, has shown positive effects in animal models of AT and tendon rupture[194]. Similarly, a combination of aligned scaffold, tendon ECM hydrogel and tendon-derived stem cells promoted Achilles tendon repair in a rabbit model[195]. Further, extracellular vesicles, often referred to as exosomes, have emerged as promising therapeutic agents for

Box 2 | Unmet needs in the design and translation of novel therapies for AT

- Complete understanding of the pathophysiological mechanisms underlying Achilles tendinopathy (AT) as well as repair and regenerative mechanisms in the Achilles tendon.
- Target disease modification and prevention of disease progression rather than treating symptoms.
- Develop suitable preclinical in vitro and in vivo models to test the effects of novel therapeutic products.
- Integrate adequate mechanical stimulation targets and regimens with the functional knowledge derived from sports medicine.
- Identify biomarkers for early detection and progression of tendinopathy, allowing for timely and targeted interventions.
- Optimize drug delivery systems for sustained and targeted release of therapeutics at the injury site, ensuring localized treatment efficacy.
- Design of optimal scaffolds that meet the mechanically demanding requirements for the Achilles tendon with appropriate resorption properties.
- Determine the optimal cell source for tendon regenerative cell therapies.
- Develop personalized therapies to adequately address patient-specific factors.
- Consider the clinical translation early in the planning process to minimize regulatory and manufacturing challenges.

Glossary

Arc sign
A clinical test used to diagnose Achilles tendinopathy. It involves identifying a tender area of intra-tendinous swelling that moves with the tendon.

Dynamometry
A method for measuring muscle strength using specialized instruments.

Enthesis
The specialized interface where the Achilles tendon attaches to bone, transitioning from soft to hard tissue to efficiently transmit mechanical loads and reduce stress concentration.

Enthesophytes
Abnormal bony outgrowths that develop at the enthesis, typically in response to chronic mechanical stress, inflammation or degenerative conditions.

Exostosis
A bony outgrowth that forms on the calcaneus (heel bone).

Function of the kinetic chain
Different body segments (that is, the ankle, knee and hip) work together to produce movement, with each segment contributing to the overall motion. In optimal circumstances, the different body segments work synergically, as links in a chain, for force transmission and energy dissipation.

Heavy-load Alfredson eccentric protocol
One of the first exercise protocols described for the exercise-based management of Achilles tendinopathy, involving 180 daily repetitions of single-leg eccentric exercises on a step with external load for the calf muscles.

Minimum clinically important difference
Smallest improvement considered worthwhile by a patient.

Plyometric exercises
Exercises involving repeated rapid eccentric and concentric contractions, optimizing movement via the stretch–shortening cycle.

Royal London Hospital test
A diagnostic test for Achilles tendinopathy, involving palpation and assessment of pain in the tendon when it is under tension.

Sever disease
A condition in children that causes heel pain due to stress on the growth plate in the heel (calcaneus), typically during periods of rapid growth.

Silbernagel protocol
Exercise-based intervention composed of various heel rise concentric–eccentric exercises that progress from double-leg to single-leg and finally to plyometric exercises, using the pain monitoring model as a guide for progression.

Stretch–shortening cycle
The process where a muscle rapidly stretches (eccentric contraction) before shortening (concentric contraction) to enhance performance, as in jumping or running.

Tendon xanthoma
A subcutaneous deposit containing lipid and cholesterol presenting as free mobile papules or as nodules on the tendon.

enhancing Achilles tendon repair[196]. These nanosized vesicles, secreted by various cell types, carry bioactive molecules such as proteins, lipids and nucleic acids that can modulate the local cellular environment and promote tissue regeneration. Studies have shown that treatment with stem cell-derived extracellular vesicles can reduce inflammation and fibrosis[197], enhance collagen synthesis and improve the overall biomechanical properties of the repaired tendon[198]. As a result, the application of extracellular vesicles is a cell-free approach in regenerative medicine, with the potential for more effective and faster tendon recovery.

The latest technological advances, such as organ-on-a-chip and bioprinting technologies, have resulted in a more sophisticated design and physiologically relevant multicellular models of tendon (patho) physiology[199–202]. These technologies will not only allow specific questions to be addressed on the role of vascularization and the immune system in the onset and development of tendinopathies, but also allow the testing of new or repurposed drugs, avoiding some of the limitations of current models[110].

Personalized and precision medicine

Another critical area to explore in tendon research is the rapid advances in personalized and precision medicine. Although certain genetic polymorphisms have been linked to an increased risk of developing AT, more comprehensive studies with larger patient numbers are needed to further substantiate this. Additionally, leveraging multiomics and other advanced technologies to define tendinopathies at a molecular level[203] will allow the precise targeting of disease subgroups based on factors such as age, physical activity, sex and genetics. Furthermore, owing to the complex aetiology of AT, additional domains beyond classic symptoms, structural alterations and functional deficits — such as psychological effects — must also be considered[183,204]. Together, these factors will aid not only in developing new advanced therapies but also in optimizing the prediction and planning of surgical procedures and physiotherapy regimens tailored to individual patients.

Rehabilitation protocols and management

There is a growing focus on standardizing rehabilitation protocols aimed at encouraging early movement to improve functional recovery. Although the adoption of pain scales has brought increased consistency to the reporting of clinical outcomes in studies, performance metrics are often overlooked or insufficiently evaluated[205]. Precision and personalized strategies anticipate the utilization of wearable devices that sense and track tendon strain and load in real-time, offering valuable insights and online feedback for patients and clinicians to personalize rehabilitation more effectively and prevent further injuries[206]. Moreover, advances in medical imaging analysis in combination with artificial intelligence tools hold the potential to revolutionize diagnosis and disease management[207].

Published online: 27 March 2025

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Acknowledgements
The authors acknowledge support from TENET COST Action CA22170 for fostering collaboration and networking opportunities. The authors thank all researchers, clinicians and physiotherapists working on Achilles tendinopathy. The authors have made every effort to cite the relevant and current literature but apologise if they have overlooked anyone or any relevant publications.

Author contributions
Introduction (A.T. and B.W.); Epidemiology (M.K. and A.S.); Mechanisms/pathophysiology (S.G.D. and J.G.S.); Diagnosis, screening and prevention (E.W. and R.S.S.), Management (R.S.S., J.G.K., J.J.B. and A.S.); Quality of life (A.S., M.K. and E.W.); Outlook (M.G.-F., M.E.G., A.T. and B.W.); overview of Primer (A.T. and B.W.).

Competing interests
J.G.K. is a consultant for Arthrex and In2Bones. The other authors declare no competing interests.

Additional information
Peer review information *Nature Reviews Disease Primers* thanks S. Rodeo, P. Kirwan, R. de Vos and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.

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