Achilles tendinopathy – pathophysiology: state of the art

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ABSTRACT
Achilles tendinopathy (AT), which is increasing in prevalence, continues to puzzle clinicians around the world. AT comprises insertional and non-insertional AT (NIAT). This review will deal with NIAT, which is often related to changes in activities in sports and occupation, but can also be unrelated to activities that load the Achilles tendon. Recent studies demonstrate that extrinsic risk factors such as errors in training and occupational activities and intake of drugs that interact in tendon metabolism may lead to tendinopathy. In combination with intrinsic risk factors, lower limb biomechanical abnormalities and metabolic, inflammatory conditions, for example, diabetes, hypercholesterolaemia and genetic deviations, the risk of AT is increased. Therefore, dysregulated mechanical loading and aberrant cellular signalling due to systemic metabolic/inflammatory imbalance and local hypoxia are suggested to cause NIAT. The exact aetiology and pathophysiology of NIAT are, however, not fully known and warrant further studies. NIAT is a condition that increases with ageing and characterised by pain during activity. Recent findings demonstrate that tenosynosis is characterised by a fibrotic, failed healing response associated with pathological ingrowth of blood vessels and sensory nerves into a normally aneuronal/avascular tendon proper. This pathological sensory nerve sprouting may partly explain increased pain signalling, and partly by release of neuronal mediators contribute to causing the fibrotic alterations observed in NIAT. Establishing the differential underlying risk factors of NIAT should give better preventive strategies in patient education and counselling. Unravelling the common pathophysiological processes of NIAT may provide the means for future targeted therapies using combined surgical and biological approaches.

INTRODUCTION
All the way back to around 400 BC, when Hippocrates first described the 'tendo magnus', which later in 1693 was named the 'Achilles tendon', has this strongest tendon in the human body remained an enigma for clinicians. Achilles tendinopathy (AT), which is the most prevalent pathological condition affecting the Achilles tendon, has an increasing incidence and constitutes a major cause for disability and decreased performance in sports as well as in the workplace (box 1).1–4

It was not until 1976 that the once believed inflammatory Achilles ‘tendinitis’ was found to exhibit histologically degenerative-like changes, which were termed ‘tendinosis’ by Puddu et al.5 In 1992, based on differential anatomical localisations and clinical pictures, AT was split into insertional and non-insertional AT (NIAT).6 The difficulties in treating AT often relate to the combination of deficient diagnostics, lack of understanding underlying aetiological factors, poor staging of the disease7 and few therapies targeted to the primary pathology (box 2).

The systematic categorisation of AT has led to insertional AT being differentiated and treated differently from NIAT. NIAT (mid-portion AT) is located around 2–7 cm from the (proximal) insertion at the calcaneus. NIAT can often be seen together with either acute or chronic paratendinopathy. Moreover, in 1998 the confusing terminology of ‘tendinitis’ and ‘overuse tendon conditions’ were changed to ‘tendinopathy’, which depicts the clinical syndrome of pain, swelling and impaired performance as in NIAT.3

We will here deal with NIAT, which is characterised by a failed healing response,6 which may exhibit a wide range of underlying factors. These can include a combination of extrinsic factors such as repetitive overload mostly using suboptimal technique, quick changes in training pattern and uneven loading, and intrinsic factors such as recently discovered genetic variants9 and different metabolic disorders, for example, diabetes mellitus.10 At first, extrinsic factors may elicit Achillodynia as a sign of functional misalignment. With time functional misaligned loading of the Achilles tendon can lead to structural changes.

In the early 21st century it was histologically established that NIAT exhibits pathological ingrowth of the nerve fibres and blood vessels into a normally aneuronal/vascular tendon proper (intrafascicular matrix),11 together with disorganisation and degeneration of collagen fibres, and increase of mucoid substance.12–15 On a cellular level repetitive loading causes tenocyte apoptosis (cell death), chondroid metaplasia, production of matrix metalloproteinases (MMPs)16 and increased expression of protective factors such as insulin-like growth factor 117 and substance P (SP).18–14 NIAT appears to be a result of an imbalance between the protective/regenerative responses and damaging/degenerative changes that result from tendon overuse and metabolic disorders (box 2).10

The understanding of NIAT continues to increase and so does the current availability of a multitude of treatment options.14 However, applying correct therapy requires knowledge of all aspects of the disorder. Therefore, this review will provide updated information on epidemiology, aetiology, anatomy, pathology and pathophysiology as a basis for understanding the disorder.

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EPIDEMIOLOGY

Incidence

The incidence of AT is increasing, especially in the developed world, and has been attributed to an escalation in sports activity both in the younger and older populations, and a general increase in the duration and intensity of training.\textsuperscript{19–21} The incidence of AT was reported as 1.85/1000 of general practitioner-registered patients based on epidemiological data from a cohort of 57725 patients in a Dutch primary care setting. In patients aged 21–60 years, however, the rate was 2.35 per 1000.\textsuperscript{22} In Finland it was found that elite long-distance runners have a lifetime risk of AT of 52%.\textsuperscript{23} The annual incidence rates of Achilles tendon disorders in top-level runners have been demonstrated around 7% and 9%.\textsuperscript{24 23}

Age

Histological studies have established that the incidence of degenerative tendinopathy increases with age. Kannus and Józsa\textsuperscript{26} found that only 30% of tendons from young, previously healthy cadavers (mean age 38 years) had histological evidence of degenerative changes, while almost half of the older cadavers (mean age 66 years) had degenerative tendinopathy. Thus, tendinopathy and osteoarthritis seem to exhibit similarities regarding increased incidence with ageing and when it comes to links to genetic predisposition and obesity.

The clear link between ageing and tendinopathy suggests changes to tendon homeostasis, which increases susceptibility to damage. Mechanisms speculated to contribute to tendinopathy with age are blood circulation,\textsuperscript{27} cellular senescence, ageing stem cell population, reactive oxygen species and formation of advanced glycation end-product (AGE) crosslinks.\textsuperscript{28} Further knowledge of age-related changes in tendon disorders is crucial to understanding increased incidence of tendon injuries in the ageing population.

Ethnicity and blood group

Ethnicity has been attributed to the development of Achilles tendon problems. Based on US military studies, the risk of Achilles tendon rupture was 3.58–13 times greater in service members of black ethnicity.\textsuperscript{29–31} Since a link between AT and increased risk of rupture has been suggested,\textsuperscript{32} ruptures may be seen as an end stage of tendinopathy. However, further studies on the association between ethnicity and tendinopathy are needed. There is little other information available about the epidemiology of Achilles tendon problems in other ethnic groups. The ABO blood group distribution of patients with an Achilles tendon rupture and of patients with AT was significantly different from the controls in a study by Kujala \textit{et al},\textsuperscript{33} with the O and A blood groups being predominant in these conditions. These populations, however, were genetically segregated.\textsuperscript{34} Both ethnicity and blood group distribution may, though, be presumed to exhibit genetic predisposition to tendinopathy.

Climate

The incidence of AT with relation to climate and seasonal changes has been investigated. Infantry recruits were found to exhibit a statistically higher incidence of AT in the winter months, with a 9.4% incidence of AT in the winter months and 3.6% in the summer.\textsuperscript{35} They attributed 94% of the cases to paratendinitis, and this was postulated to be due to a fall in the temperature of the Achilles paratenon, resulting in decreased lubrication and increased friction.

Activity

Achilles tendinopathy and ruptures have strong associations with increased sports activity. The incidence of AT has been demonstrated higher in individuals who start a new or unaccustomed activity, in runners and badminton players, and in sportsmen who increase their training load, change their shoes or change their usual running surfaces. The incidence of sports-related AT has been reported to be higher than in the rest of the population (box 3).\textsuperscript{36}

New military recruits and officer cadets exhibit an incidence of AT of 6.8%–14.5%, which is believed to be due to unaccustomed activity.\textsuperscript{37,38} Top-level runners exhibit an annual incidence of 7%–9% of AT.\textsuperscript{24 25} The lifetime risk of AT in former elite male distance runners is between 52% and 56.6%,\textsuperscript{39 40} and 34% in middle-distance runners.\textsuperscript{39} The incidence of AT before the age of 45 has also been shown to be high for middle-distance

Box 1 Key historical evolution of Achilles tendon pathology terminology

- In c 460–370 BC Hippocrates described ‘tendo magnus’.
- In 1693 a Dutch surgeon, Philip Verheyen, named the ‘Achilles tendon’, according to the legend.*
- In 1976 Puddu \textit{et al}\textsuperscript{*} redefined the term tendinosis based on histological findings of degenerative changes and failed healing.
- In 1992 Achilles ‘tendinitis’ was split into insertional and non-insertional Achilles tendinopathy.\textsuperscript{6}
- In 1998 the term Achilles ‘tendinopathy’ was defined as the clinical syndrome of pain, swelling and impaired performance.\textsuperscript{7}
- In 2011 a structured terminology for Achilles tendon pathology was described.\textsuperscript{29}

*According to the legend, Achilles, the hero and great warrior in Homer’s Iliad, was born in c 12–13th century BC and dipped into the river Styx, but not his Achilles tendon. Thereafter, Achilles became immortal with one exception…his heel.

Box 2 Key articles

- Definition of tendinosis.\textsuperscript{5}
- Ageing increases tendinosis.\textsuperscript{36}
- Achilles ‘tendinopathy’—clinical syndrome of pain, swelling and impaired performance.\textsuperscript{8}
- Achilles ‘tendinopathy’ is split into insertional and non-insertional Achilles tendinopathy.\textsuperscript{6}
- Achilles tendon homeostasis is regulated by loading and cellular activity. Loading has two phases: (1) catabolic and (2) anabolic. Repetitive loading can cause too much catabolic activity.\textsuperscript{90}
- Tendon stem cells are identified.\textsuperscript{57}
- Repetitive loading causes, on a cellular level, tenocyte apoptosis, chondroid metaplasia and production of matrix metalloproteinase enzymes, which cause collagen and proteoglycan degradation.\textsuperscript{13}
- Achilles tendinopathy exhibits a pathological ingrowth of sensory nerves into a normally aeuronal/avascular tendon proper. Nerve sprouting may partly explain pain signalling and partly, by release of neuronal mediators, contribute to causing fibrotic alterations.\textsuperscript{88}


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Box 3 Epidemiology

- Incidence: Achilles tendinopathy occurs in around 1.85–2.35/1000 patients.
- Ageing: increases histological signs of tendinosis.
- Ethnicity and blood group: predisposition suggests genetic links to tendinopathy.
- Climate: association with cold weather suggests susceptibility to extrinsic factors.
- Activity: the association with new or unaccustomed activities, increase in training load, change in, for example, shoes, or change in, for example, usual running surfaces, should all be considered when counselling patients.

Box 4 Tips and tricks

Ask/investigate the patient for:
- Intrinsic, metabolic risk factors: for example, diabetes, hypercholesterolaemia, inflammatory disorders and others.
- Extrinsic, intake of drugs, such as corticosteroids, aromatase inhibitors, statins and quinolone antibiotics.
- Extrinsic mechanical risk factors, for example, excessive mechanical overload, training errors and so on.

Examine the patient for:
- Intrinsic biomechanical risk factors such as leg length discrepancy, joint deformities and so on.

and long-distance runners (adjusted OR of 31.2) compared with controls.\

The cumulative running load has been correlated with the incidence of AT. AT was significantly and positively correlated with age, weekly mileage and previous jogging injury.\(^{41}\) Patients with AT had longer exposure time, with significantly more years of training and significantly longer distances per week than those without tendinopathy.\(^{39}\) Overtraining was found to be the most common cause of overuse AT in runners (75.2%).\(^{24}\)

AETIOLOGY

The risk factors of NIAT can be categorised as intrinsic and/or extrinsic factors (figure 1). Some of the proposed intrinsic factors include biomechanical abnormalities of the lower extremity such as leg length discrepancy, hyperpronation, varus deformity of the forefoot, pes cavus and limited mobility of the subtalar joint.\(^{42}\) Intrinsic risk factors of NIAT additionally include systemic, metabolic-related disorders such as diabetes, obesity, hypercholesterolaemia, hyperuricaemia, inflammatory disorders and genetic variants (box 4).\(^{10}\)

Extrinsic factors include excessive mechanical overload and training errors such as increased internal training, abrupt changes in scheduling, excessive hill training, training on hard or sloping surfaces, increased mileage, increased repetitive loading, poor shock absorption, and wedging from uneven wear.\(^{2,44}\) Moreover, certain drugs are known to increase the risk of NIAT, such as corticosteroids, aromatase inhibitors, quinolone antibiotics and statins (box 4).\(^{44}\)

Intrinsic

Diabetes

Pre-diabetes and diabetes mellitus both exhibit known harmful effects on tendon homeostasis and tendon healing.\(^{45,46}\) Diabetes leads to halted capability of regeneration in the tendon.\(^{45,46}\) It has been demonstrated that diabetes/pre-diabetes causes changes in Achilles tendon mRNA expression of collagens, MMP and various inflammatory and growth mediators.\(^{45,47,48}\) Diabetes mellitus also affects the mechanical properties of the musculo-tendinous complex, and additionally is speculated to increase the risk of fracture. Recently it was demonstrated that AGEs, which crosslink with collagen extracellular matrix (ECM),\(^{48}\) accumulate in the Achilles tendons with intake of an AGE-rich diet.\(^{49}\) These findings suggest that food-derived AGEs may alter tendon properties and increase the risk of NIAT.

Hypercholesterolaemia

Hypercholesterolaemia is often observed in patients with diabetes mellitus, but exists as a separate risk factor for tendinopathy.\(^{50}\) Hypercholesterolaemia occurs both as hereditary dyslipidaemias as well as a result of lifestyle. High cholesterol has been shown to alter tendon biomechanical properties. However, only a few pathomechanisms have yet been demonstrated, such as dysfunctional local ECM composition and turnover, altered protein synthesis and inflammatory gene expression.\(^{50}\)

Obesity

In addition to hypercholesterolaemia, obesity has been demonstrated to be a separate risk factor for tendinopathy.\(^{51}\) Furthermore, tendinopathy treatment also appears to exhibit poorer outcomes among obese individuals. The pathogenesis is multifactorial and includes overload, related to the increased body mass index, but also systemic factors such as bioactive peptides (eg, chemerin, leptin, adiponectin). These bioactive peptides elicit a chronic and low-grade inflammation, which can give rise to metabolic syndrome.\(^{52}\) Obesity in AT is one factor that should be assessed and treated. Further studies, however, should be performed to establish the real strength of the association between NIAT and diabetes mellitus, hypercholesterolaemia and obesity.\(^{51}\)

Hyperuricaemia

Hyperuricaemia is a diagnosis which is easy to miss but can lead to repeated occurrence of tendinopathy.\(^{53}\) Crystal depositions caused by monosodium urate and hyperuricaemia elicit inflammation in the tendon. At present, however, more research is needed regarding
the diagnostics of uricaemia in tendinopathy and whether hyperuricaemia could be a target for treatment of NIATs.

Inflammation

Whether inflammation is a risk factor in tendon disorders has long been a subject of considerable debate.54 Advances in our understanding of the pathophysiological pathways of inflammation have provided further insight into its potential role in specific forms of tendon disease.52 Specific circumstances such as extreme mechanical stress on the Achilles tendon in combination with systemic inflammation may potentiate the development of tendinopathy.53

Exogenous inducers of inflammation comprise microbial and non-microbial foreign bodies, toxins and allergens. Crystal formations such as urate and calcium pyrophosphate, collagen products such as AGE, and products of ECM breakdown constitute some of the few known endogenous initiators of inflammation.60 These different triggers can lead to neutrophil, macrophage and mast cell activation, and subsequently to the production of mediators of inflammation. Increased levels of proinflammatory mediators including interleukins (IL-1, IL-6) and neuropeptides (SP) have been found in tendinopathy.54,55

Increasing evidence demonstrates that inflammatory pathomechanisms and the immune system are activated in the tendon matrix during tissue injury and dysregulated homeostasis. Tendon remodelling is regulated by several essential mediators including cytokines, which dictate cell type and tissue specificity of responses that ultimately balance a reparative versus degenerative process. Proinflammatory mediators including tumour necrosis factor α, prostaglandin E2 (PGE2) and leucotriene B4 are seen specifically in obesity. This correlates with a broader view of ‘tissue stress’—effects of chronic inflammation.54

Genetic disorders

Genetic abnormalities have been demonstrated common in the normal population, whereby small genetic variations can cause increased susceptibility of sustaining a tendon injury.9 To date, around 18 gene intervals and 32 polymorphisms induce collagen isoforms and changes in matrix structure, which are related with increased risk of tendon pathologies.6,16

Other genetic disorders that affect tendon, for example familial hypercholesterolaemia, entail genetic defects leading to metabolic disorders.57 Thus, familial hypercholesterolaemia causes tendon xanthomas and alkaptonuria, leading to acid accumulation observed as ochre/yellow pigmentation (ochronosis) in the tendon. Presumably, many more genetic alterations exist which cause increased risk of tendinopathy.

Extrinsic

The extrinsic risk factors for AT have been suggested to include poor technique, previous injuries, changes in training pattern, footwear, and environmental factors such as training on hard, slippery or slanting surfaces. Excessive loading of the tendons during vigorous physical exercise is regarded as the main pathological stimulus for tendinopathy,43 presumably as a result of imbalance between muscle power and tendon elasticity. The AT may respond to supraphysiological overloading and to repetitive physiological load by either inflammation of its sheath, and most-often secondarily by degeneration of its body or a combination of both.58,59

Drugs

One risk factor for tendon disorders, which is often underestimated, is the intake of various medications,44 which can cause harmful adverse effects, such as tendinopathy and tendon ruptures. Medications associated with tendon disorders are corticosteroids, quinolone antibiotics,60 aromatase inhibitors (oestrogen inhibitors) and statins.

Specifically corticosteroids (glucocorticoids) are yet commonly used to alleviate several musculoskeletal disorders. Corticosteroids, however, exert harmful effects on tendon metabolism.61 Glucocorticoids inhibit tendon cell proliferation, inhibit synthesis of ECM, cause inflammation and collagen disorganisation, and derange the mechanical properties of the tendons. Thus, corticosteroids are harmful for the tendons and not a first line of treatment for NIAT.

ANATOMY

Macrostructure

The Achilles tendon originates from the merging of the soleus muscle (from the tibia and fibula) with the two bellies of the gastrocnemius (from femur), and it is inserted distally onto the calcaneus. The medial head of the gastrocnemius arises from the medial condyle of the femur, slightly larger and extends a little more distally than the lateral head, which arises from the lateral femur condyle. In approximately 7–20% of the population, the plantaris tendon, which primarily lies on the medial side of the Achilles tendon, is absent or according to recent findings may exhibit another anatomical pathway.62 The plantaris tendon is also suggested to play a role in complaints in patients with mid-portion AT.62 One study on patients reoperated on because of persisting medial pain on NIAT found invaginated or enlarged plantaris tendons in 58 of 73 (80%) cases.63

The collagen fibres of the Achilles tendon rotate 90° during its descent, such that the fibres that lie medially in the proximal portion become more posterior further distally. The rotating configuration of the Achilles tendon contributes to the elongation and elastic recoiling within the tendon.64

The Achilles tendon, which has a length of around 15 cm from the musculotendinous junction to the calcaneal insertion, is the strongest tendon in the body and can resist forces of up to 9 kN (12 times the weight of the body) during running.65

Microstructure

The Achilles tendon microstructure is optimised to fulfil the functional role, with abundant and highly aligned collagen fibres producing the highest tensile strength required for efficient force transfer. The strength of the Achilles tendon is partly explained by the composition, which is made up mainly of the strong collagen type I that accounts for up to 80% of its dry weight. The collagen, which is embedded in a proteoglycan-water matrix, is produced by tenoblasts and tenocytes that lie between the collagen fibres in a complex structure.66 Therefore, it is easily understood that disturbances anywhere from the collagen producing cells to the assembly of collagen fibres, fascicles and bundles can cause tendon pathologies. Recently, stem cells have been isolated from tendon tissues.57 The identification of these so-called tendon-derived stem cells gives new implications in the regulation of tendon homeostasis and tendinopathy.

Innervation and blood supply

The innervation of the Achilles tendon comes from the contributing muscles, from the nervus suralis and also from nearby cutaneous nerves, and the blood supply emerges from mainly two arteries, the posterior tibial and the peroneal arteries. The innervation and blood supply of a healthy Achilles tendon come from the structures surrounding the tendon proper, that is,
the interfascicular matrix, while the tendon proper, that is, the intrafascicular matrix, is essentially lacking innervation (figure 2). This anatomy of the tendon suggests that the metabolism and inflammatory reactions are regulated from the tendon envelope, that is, interfascicular matrix.15

Moreover, the mid-substance of the Achilles tendon approximately 3–6 cm proximal to the calcaneal bone insertion, which is sparsely vascularised, is affected by tendinopathy and subsequent rupture. This area is also devoid of neuronal supply, leading to a vulnerable area in the tendon in terms of reparative (adaptive) capacity to meet repetitive mechanical stress in combination with poor metabolic control (poor microcirculation).27

Metabolic activity and tissue adaptation
Tendons exhibit an oxygen consumption that is 7.5 times lower than that of the skeletal muscle. Therefore, tendon metabolism is scanty in comparison with other tissues. Mechanical loading is the major regulatory factor of tendon metabolism. Following loading/unloading, mechanotransduction and molecular anabolic/catabolic signalling result in tissue adaptations in the tendon, which particularly during youth and adolescence (growth and maturation) produce tendon size adjustments.68 This adaptive response varies in different anatomical parts of the tendon. For example if a person quickly builds a large muscle belly, this may have a negative impact on the tendon, which takes longer time to adapt to new loading situations. This is dramatically seen in patients who abuse growth hormones, which are more prone to tendon rupture due to the possible imbalance between the force exerted by a hypertrophic muscle contraction and the tendon.69

Tendinous tissue adheres to the paradigm ‘use it or lose it’. Therefore, tendons need homogeneous loading to preserve their functioning set point. While ligaments are passive structures, tendons are active connective tissues and often work near their mechanical limit, which suggest an exposure to higher risks for damage.68 70 These types of risks may lead to compromised function, pain and impaired repair mechanisms when impacted by repetitive loading in combination with metabolic derangements. That is, metabolic disorders can exacerbate the risks of developing tendon disorders such as AT.

PATHOLOGY
Macrostructure
Intact healthy tendons are glistening white, fibroelastic and tolerate high load. Tendinopathic tendons are greyish, irregular in form and have an increased risk of rupture (box 5).26

Microstructure
The microstructural changes in tendinopathy, observed on histological examination, are categorised as tendinosis and mostly include hypocellularity/hypercellularity, irregular collagen structure, and increased ingrowth of nerve fibres and blood vessels (figures 3 and 4).

Collagen fibres in tendinosis are observed as disorientated and disorganised, and the fibres are separated. The collagen composition in tendinosis constitutes an increased ratio of type III versus type I collagen as compared with healthy tendons. This characteristic results in an increased risk of tendon rupture, since type III collagen is not as strong as type I collagen.13

Box 5 Key issues of patient selection
The best user independent visualisation of the pathoanatomical features of non-insertional Achilles tendinopathy (NIAT) is attained by the use of MRI. The best accessible and practical visualisation of the pathoanatomical features of NIAT, however user-dependent, is achieved by the use of Doppler ultrasound (US).

▶ Failure to demonstrate neovascularisation on US does not reject the diagnosis of NIAT.
There is a large variation in cell density in tendinopathy, which is thought to be due to the different phases of tendinosis development. Hypercellular areas of tenocytes, with rounded nuclei, may produce proteoglycans and proteins as a proliferative healing response in the injured tendon. Other areas of the tendon may, in contrast, contain fewer tenocytes than normal. Hypocellularity is associated with the process of apoptosis in tendinosis, which may be linked to a remodelling stage of healing. Thus, tendon pathology may be better understood as a continuum.

Myofibroblast-like synoviocytes and chondrocytes can be observed to a greater extent in tendinosis. Furthermore, an increased number of endothelial cells is observed, which participate in neoangiogenesis formation. However, the amount of inflammatory cells in tendinosis is still debated. On the whole, inflammatory cell infiltration is not a main characteristic of tendinosis, at least in the proper tendon substance. In different phases of tendinopathy (and subsequent failed healing response), however, infiltration of lymphocytes and macrophage-type cells may be observed reflecting an inflammatory healing process. Moreover, tendon-derived stem cells can be recruited to the site of repair or tendinopathy. Dysregulation in tendon-derived stem cell differentiation has been suggested as a pathway in tendinopathy development. To date, however, the exact cellular and molecular processes involved in the dysregulation of the healing process, leading to tendinopathy, are not fully known.

**Neoangiogenesis**

Neoangiogenesis is a common feature observed in tendinosis and is used clinically as part of the diagnostic criteria of AT when using colour Doppler ultrasonography. Neovascularisation may prove to be a response to a suggested hypoxic environment in tendinosis and hence comprises a more progressed state of tendinopathy. Interestingly, colour Doppler sonography has shown decreased neovascularisation following eccentric training treatment programme. Neoangiogenesis has, however, also been questioned to give no additional value in diagnostics, no firm
State of the Art

Figure 5 Pathophysiology. The pathophysiology of non-insertional Achilles tendinopathy (NIAT) may be elicited by intrinsic and/or extrinsic risk factors. The risk factors may lead to mechanical and cellular dysregulations together with lack or excess of signal substances, which triggers tendinopathic alterations.

prognostic value and no proven relation with symptoms. Hence, still a lot of high-quality research is needed.

Neoinnervation

Ingrowth of sensory nerve fibres into the intrafascicular matrix has been repeatedly demonstrated in tendinopathy (figure 4). Under normal, healthy, conditions nerve fibres do not enter the tendon proper. The nerve ingrowth in tendinopathy can exist both colocalised with the blood vessel as well as in the form of neoinnervation without vascular coexistence.

Given the knowledge of extensive blood vessel and nerve ingrowth that occurs into the tendon proper of AT, new therapies may follow. Neoinnervation, however, is also to a different extent integrated with changes in signal substances and pain receptors, which will change pain sensitivity; this is further discussed in the Pathophysiology section.

The integrated action of the neurovascular system in AT is an emerging research field that may prove to deliver both molecular and clinical targets for future therapies. Given this knowledge it is easy to understand that recent clinical therapies of NIAT target the ‘envelope’, that is, paratenon, which is the main regulatory site (figure 2).

PATHOPHYSIOLOGY

Homeostasis

Mechanical loading is the main regulator of tendon homeostasis, followed by tendon cell activity, which is regulated by neuronal and cellular mediators (figure 5). These mediators can be produced locally by nearby cells or remotely and transported via blood circulation or nerve supply. Therefore, a combination of mechanical and cellular dysregulations together with lack or excess of signal substances may lead to tendinopathy.

Loading

Weightbearing with mechanical loading of tendinous tissue elicits an anabolic upregulation of collagen gene expression and elevated synthesis of collagen proteins. Collagen synthesis peaks around 24 hours after exercise and remains elevated for up to 70–80 hours. Exercise additionally causes degradation of collagen proteins. However, the timing of this catabolic peak occurs earlier than the anabolic peak. The consequences are net losses of collagen around the first 24–36 hours after training—followed by a net gain in collagen. Therefore a restoration time interval in between exercise bouts is critical for tissue adaptation and avoidance of a net catabolic situation. The time of adaptation to new exercises or loading is also associated to the specific anatomical structures in the tendon.

Inflammation

Loading that occurs in a repetitive manner causes the tenocytes to produce inflammatory molecules and increases the risk of microruptures of collagen fibrils. Elevated levels of inflammatory mediators such as PGE2 have been found in tendons after repetitive mechanical loading. Experimental injections of PGE2 into the tendon proper resulted in degenerative changes, and peritendinous injections of PGE1 causes tendinopathy on histological examination. Hence, many studies verify that inflammation plays an important role in the development of tendinopathy. Tendinopathy demonstrates granulation alterations of capillary vessels and an inflammatory infiltrate consisting of macrophages, mast cells, and B and T lymphocytes. Observations like these reflect that the intrinsic immune system has a regulatory role in early tendinopathy. A number of proinflammatory cytokines, for example, IL-18, IL-15 and IL-6, have been detected in tendinopathy.

Macrophages play an essential role in orchestrating inflammation and tissue repair. Signalling pathways activate macrophages to become either M1 (proinflammatory) or M2 (anti-inflammatory) subtypes. Several signalling pathways such as interferons, nuclear factor κB and glucocorticoid receptor activation pathways are involved in determining the M1 or M2 pathway. Thus, inflammatory pathways in tendinopathy may change macrophage subtypes, leading to failed, fibrotic, healing responses.
Tenocytes and fibroblasts, which are subjected to repetitive mechanical stress in combination with signals from the transforming growth factor β (TGF-β) and proinflammatory cytokines, can transform into myofibroblasts. Myofibroblasts exhibit important roles in tendon healing, presumably also as a mechanism fails, the myofibroblasts will propagate a hyperproliferative process, resulting in fibrosis, which is observed as a prominent histological feature of tendinopathy (figure 3).

**Hypoxia**

Tendinopathy demonstrates hypoxic changes on histopathology and increased levels of lactate, which suggest that hypoxia is a regulatory mechanism underlying tendinosis development. Hypoxia may cause fibroblast hyperproliferation and stimulate upregulation of MMPs, which causes altered material properties of the tendon. Certain MMPs, such as MMP-9 and MMP-13, are also upregulated by high glucose levels, which also suppress tendon-derived stem cells. Moreover, hypoxia is involved in the regulation that converts the production of collagen type I into type III and increases ECM production. Furthermore, hypoxia upregulates the mRNA expression of the vascular endothelial growth factor (VEGF), leading to increased microvessel ingrowth (neoangiogenesis) into the tendon—a main finding in tendinopathy (figure 3).

**Vascular endothelial growth factor**

Hypoxia, as well as mechanical strain and growth factors, regulates neoangiogenesis. VEGF stimulates endothelial cell migration in wound healing by inducing chemotaxis and vasodilatation. VEGF stimulates the production of integrins that are chemotactic for endothelial cells, and moreover increases vascular permeability and prevents apoptosis.

Neovascularisation in tendinosis has been demonstrated to induce deteriorated mechanical properties of the tendon and may therefore be a contributing factor to rupture. Neoangiogenesis has also been speculated to cause pain since sclerotherapy has demonstrated some partial pain mitigation in tendinopathy. Blood vessels per se, however, are not painful. Rather spouting and ingrowth of sensory nerve fibres, which often but not always follow neoangiogenesis into the tendon proper in patients with tendinopathy, elicit and modulate pain responses (figure 4). It has been demonstrated that neoinnervation can occur without angiogenesis.

Interestingly, however, there is a close connection between the neuronal and vascular systems. Hence, the nerve factors SP and nerve growth factor (NGF) stimulate angiogenesis. SP moreover induces neoangiogenesis by stimulating endothelial cell proliferation and NGF promotes neovascularisation partly via stimulation of VEGF.

### Neurotrophic substances

Since ingrowth of sensory nerves from the enveloping structures, for example, paratenon, into the tendon proper is characteristic of tendinopathy, it is suggested that neurotrophic substances are involved in this dysregulation. NGF and brain-derived neurotrophic factor have been demonstrated in the tendon and are dysregulated in metabolic disorders such as diabetes mellitus.

Interestingly, neurotrophic factors may therefore be involved in the neoinnervation in tendinopathy, which is seen as a reaction to both repetitive loading and to injury. Sensory nerve ingrowth, which is seen in normal tendon repair, is associated with increased nociception. After healing, nerve retraction is correlated with decreased nociception. In tendinopathy, however, the ingrown sensory nerves do not retract, as in normal healing. Therefore, the dysregulated aberrant sprouting of the sensory nerve fibres may reflect a failed healing response (figure 4), causing increased pain signalling and possibly also contributing to the hyperproliferative alterations seen in tendinosis.

Interestingly, the concept of neoinnervation and neoangiogenesis in relation to chronic pain conditions is not only confined to tendons. Intervertebral discs are, during healthy circumstances, aneural in the nucleus pulposus, similarly to the tendon proper. Degenerative intervertebral discs, however, also exhibit neoinnervation of the nerves, colocalised with NGF, entering through the vertebral endplates into the nucleus pulposus.

### Signal substances

Peripheral nerve fibres transmit pain and additionally react to mechanical stimuli by releasing various signal substances. The mediators released by nerves are normally controlling tendon homeostasis and healing, but can during prolonged release cause fibrosis due to their proliferative actions and potentiate pain signalling. The presence of neuronal signal substances in the tendon has been established almost 20 years ago. Today, a complex operative system of neuronal mediators and receptors has been found in the tendon.

Tendinopathic tendons exhibit elevated occurrence of SP, which in addition to its role in nociception may reflect proinflammatory and trophic actions (figure 4). SP is known to regulate vasodilation, plasma extravasation and release of cytokines by binding to its receptor, neurokinin 1, which is present in the tendon and upregulated by loading. SP induces proliferation of fibroblasts and endothelial cells, and promotes transformation of fibroblasts into myofibroblasts by stimulating the production of signal substances.

**Box 6 Essential and/or typical features of non-insertional Achilles tendinopathy (NIAT)**

- **Introduction**
  - a. Differentiate NIAT from insertional Achilles tendinopathy.
- **Epidemiology**
  - a. Sudden and high increase in the duration and intensity of training.
- **Aetiology**
  - a. Intrinsic factors: lower limb biomechanical abnormalities and metabolic, inflammatory conditions, for example, diabetes, hypercholesterolaemia and genetic variants.
  - b. Extrinsic factors: training errors and intake of certain drugs.
- **Anatomy**
  - a. Complex macrostructural and microstructural anatomy, including poor microcirculation and increase susceptibility to tendinopathy.
- **Pathology**
  - a. Hypercellularity, irregular collagen structure and increased collagen type III/I ratio, neovascularisation and neoinnervation.
- **Pathophysiology**
  - a. A dysregulated mechanical loading and/or cellular signalling due to systemic metabolic/inflammatory imbalance and local hypoxia.
Major pitfalls of Achilles tendinopathy: pathophysiology

- In the diagnosis and prevention of non-insertional Achilles tendinopathy (NIAT), we suggest to systematically address and educate patients about the following:
  - Newly identified intrinsic risk factors such as:
    - Diabetes, obesity, hypercholesterolaemia, hyperuricaemia, inflammatory disorders, genetic variants and so on.
  - As well as known intrinsic risk factors, for example:
    - Biomechanical abnormalities of the lower extremity such as leg length discrepancy, hyperpronation, varus deformity of the forefoot, pes cavus and limited mobility of the subtalar joint.
  - Recently identified extrinsic risk factors such as:
    - Corticosteroids, aromatase inhibitors, statins and quinolone antibiotics.
  - Known extrinsic risk factors, for example:
    - Excessive mechanical overload and training errors such as increased interval training, abrupt changes in scheduling, excessive hill training, training on hard or sloping surfaces, increased mileage, increased repetitive loading, poor shock absorption, and wedging from uneven wear.

- Understanding the pathophysiological processes of NIAT will provide the means to correctly use future targeted therapies consisting of combined surgical and biological approaches.

of TGF-β. SP can furthermore recruit tendon-derived stem cells to sites of repair or tendinopathy. Hence, abnormal increase in SP possibly contributes to tendinosis, that is, fibrotic changes, observed in patients with tendinopathy, such as tenocyte transformation, hypercellularity and neovascularisation. Another nerve factor, which is highly upregulated in tendinopathy, is the neurotransmitter glutamate. Upregulated levels of glutamate in tendinopathy were found not to be correlated to tendon pain. The glutamate receptors, however, may regulate pain in tendinopathy.

Receptors

When it comes to receptors implicated in various painful disorders, N-methyl-D-aspartate receptor type 1 (NMDAR1) (glutamate receptor) is one of the most essential. An increase in glutamate signalling has just lately been established in patients with tendinopathy, with the specific localisation suggesting a particular pathological role. The upregulated occurrence of glutamate/NMDAR1 was observed in morphologically transformed tenocytes, in ingrown sprouting nerve fibres, and in the endothelial and adventitial layers of the neovessel walls.

NMDAR1 can become activated (phospho-NMDAR1), for example, to become more pain-inducing, by loosing the stabilising magnesium, which blocks the ion channel. Phospho-NMDAR1 was observed in the tendon proper of tendinopathic biopsies, but not in the control tendon, suggesting a role in pathological tenocyte transformation, neoangiogenesis and pain signalling. Hence, targeted blocking of NMDAR1 could be a means of mitigating the symptoms of tendinopathy. Further investigations of the neuronal and nociceptor pathophysiology in tendinopathy may lead to novel therapies.

FUTURE PERSPECTIVES

NIAT negatively affects the quality and function of millions of people. Evidence-based targeted therapies for NIAT have been unsatisfactory due to poor understanding of the underlying pathology and pathophysiology (boxes 6 and 7).

Recent advances in the understanding of the differential aetiologies of NIAT both related to loading activities but also unrelated to repetitive loading have unravelled metabolic risk factors, which are essential to address in a systematic manner during patient counselling. The new knowledge should be implemented for better patient education.

Further mapping of the molecular pathways involved in the common pathophysiological processes of NIAT may provide means for future targeted therapies using combined surgical and biological approaches. Tissue engineering and tissue regeneration with stem cells appear as promising new techniques to address tendon repair.

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