

## Topical Review

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# Tendon pain – what are the mechanisms behind it?

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### Abstract

**Objectives:** Management of chronic tendon pain is difficult and controversial. This is due to poor knowledge of the underlying pathophysiology of chronic tendon pain, primarily known as tendinitis but now termed tendinopathy. The objective of this topical review was to synthesize evolving information of mechanisms in tendon pain, using a comprehensive search of the available literature on this topic.

**Content:** This review found no correlations between tendon degeneration, collagen separation or neovascularization and chronic tendon pain. The synthesis demonstrated that chronic tendon pain, however, is characterized by excessive nerve sprouting with ingrowth in the tendon proper, which corresponds to alterations observed also in other connective tissues of chronic pain conditions. Healthy, painfree tendons are devoid of nerve fibers in the tendon proper, while innervation is confined to tendon surrounding structures, such as sheaths. Chronic painful tendons exhibit elevated amounts of pain neuromediators, such as

glutamate and substance p as well as up-regulated expression and excitability of pain receptors, such as the glutamate receptor NMDAR1 and the SP receptor NK1, found on ingrown nerves and immune cells. Increasing evidence indicates that mast cells serve as an important link between the peripheral nervous system and the immune systems resulting in so called neurogenic inflammation.

**Summary:** Chronic painful tendons exhibit (1) protracted ingrowth of sensory nerves (2) elevated pain mediator levels and (3) up-regulated expression and excitability of pain receptors, participating in (4) neuro-immune pathways involved in pain regulation. Current treatments that entail the highest scientific evidence to mitigate chronic tendon pain include eccentric exercises and extracorporeal shockwave, which both target peripheral reinnervation aiming at nerve regeneration.

**Outlook:** Potential mechanism-based pharmacological treatment approaches could be developed by blocking promoters of nerve ingrowth, such as NGF, and promoting inhibitors of nerve ingrowth, like semaphorins, as well as blocking glutamate-NMDA-receptor pathways, which are prominent in chronic tendon pain.

**Keywords:** mast cells; nerve tissue proteins; neuronal plasticity; pain; receptors; tendon.

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## Introduction

Chronic tendon pain is a common disabling condition that affects the quality of life for millions of people, leading particularly to impaired limb function and reduced physical activity [1], thus impacting the general health condition of patients [1–4]. Still today, we do not have any effective pharmacological treatments, the main reason being that the underlying pathophysiology of chronic tendon pain has been largely unclear.

Chronic tendon pain is included in the terminology of tendinopathy [1, 5]. Tendinopathy was formerly known as “tendinitis” [6, 7]. However, the etiological origin of inflammation has been questioned over the years and therefore in 1998 the confusing terminology of “tendinitis”

was changed to tendinopathy [8]. Tendinopathy depicts the clinical syndrome of swelling, pain and impaired performance, with chronic pain being the predominant symptom [1].

There are more than 1,000 tendons in our body that potentially can present with chronic tendon pain. Common localizations of tendinopathy include the upper extremities, which are more often affected in work-related situations, whereas tendinopathy of the lower extremities more frequently is related to sports activities (Table 1). Interestingly, chronic tendon pain may evolve also without repetitive loading and therefore a deeper causal understanding is warranted.

The diagnosis of tendinopathy is mostly based on a careful medical history and detailed clinical examination with the aim to determine whether the tendon is the source of pain. Pain induced by loading and stretching of the tendon is pathognomonic for tendinopathy [9].

Diagnostic imaging is mostly used for differential diagnosis, and will not tell whether the tendon is causing pain or not [10]. MRI and ultrasound may depict pathological tissue alterations commonly seen in tendinopathy such as swelling, thickening and increased vascularity. However, tendon pathology displayed on imaging may in individual cases have no correlation to the patient's symptoms [10].

Establishing the diagnosis of tendinopathy also includes assessments of intrinsic and extrinsic risk factors [2]. Intrinsic factors include biomechanical abnormalities, e.g., limited joint mobility, and systemic, metabolically related disorders such as diabetes, obesity, hypercholesterolemia, inflammatory disorders, and genetic variants [2]. Extrinsic factors include excessive and uneven mechanical loading due to training or work [5, 11]. Moreover, certain drugs, such as corticosteroids, aromatase inhibitors, quinolone antibiotics and statins [12], are known to increase the risk of developing tendinopathy. Therefore, it is essential to be aware and if possible to avoid these drugs and especially combinations of e.g., corticosteroids and quinolones. Accordingly, in- and extrinsic factors must be excluded or handled as part of diagnostics and treatment of tendinopathy [2].

Several hundreds of different treatments have been suggested for chronic tendon pain [1, 13]. However, most treatments are lacking in efficacy for pain relief, the reason being that most treatments are not addressing the underlying pathophysiological mechanisms of tendon pain. Thus, in order to cope with this disappointing situation and improve efficacy for pain relief, treatments must target the actual pain mechanisms in tendons.

The aim of this current topical review was to document and present the pathophysiological mechanisms of action, pain receptors and mediators underlying the development of chronic tendon pain that have recently been identified. This new understanding may allow us to develop new targeted treatments for managing tendon pain.

## Methods

The aim of this topical review was to examine the five etiological theories for tendon pain that have been postulated: degeneration, collagen separation, neovascularization, neurogenic source, neuro-immune connection. This was performed by posing the following questions: (1). Do histologic or radiographic findings correlate to tendon pain? (2). Does neovascularization correlate to tendon pain? (3). Does tendon neuroanatomy correlate to tendon pain? (4). Is there a neuro-inflammatory immune connection in tendon pain? Only original articles about chronic tendon pain and tendinopathy were included. The Web of Science, Scopus and PubMed/MEDLINE databases were searched up to May 26, 2021 using combined terms related to tendon, injury and pain. The following MESH-terms were used: tendon; tendinopathy; rupture; pain; pain mechanism; degeneration; collagen separation; neovascularization; neurogenic; nerve; immune, and a search string was constructed. We additionally used review articles to check that relevant articles were included. Articles in other languages than English were excluded. Identified records were screened by AA and PA according to the eligibility of the aim. Articles were first screened for eligibility based on their title, and then, if needed, based on full text. We then performed a narrative synthesis of this extracted data. The extracted articles were grouped into the five postulated etiological theories for chronic tendon pain. The acquired material was synthesized into relevant underlying mechanism related to chronic tendon pain.

## Results

### Do histologic or radiographic findings correlate to tendon pain?

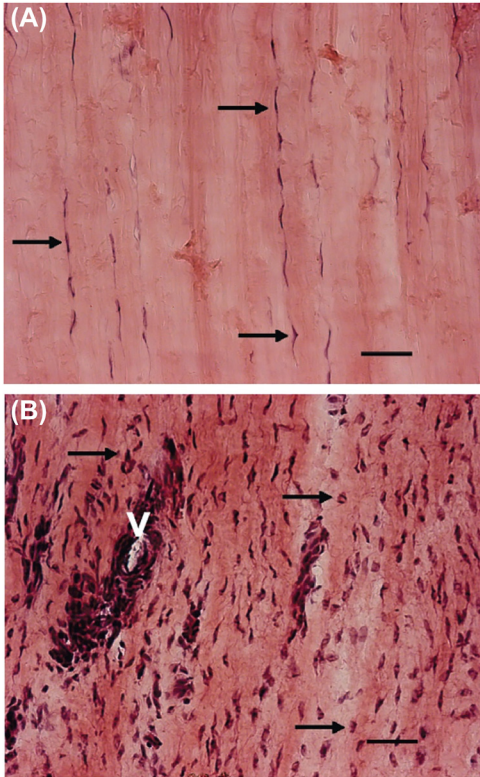
Histologically, tendinopathy may display degenerative changes such as disorganization of collagen fibers, increase of collagen type III, increase of extracellular matrix and blood vessel ingrowth into the tendon proper (Figure 1). However, these aforementioned tissue pathologies may also be exhibited in asymptomatic persons [10, 14, 15]. In addition, patients can recover from chronic tendon pain without reversal of imaging-identified tendon pathology [10].

Collagen separation is neither correlated with tendon pain since large asymptomatic ultrasonographic hypoechoic regions (i.e., abnormal collagen) can be found in tendons without a history of pain [16, 17]. Thus, tendon degeneration and separation are not directly

**Table 1:** Twenty-five of the most common tendons with chronic pain.

<b>Pain inUpperextremities</b>	<b>Pain location</b>	<b>Tendon</b>	<b>Diagnosis</b>	<b>Risk factors</b>
Shoulder	Lateral	Supraspinatus (SP)	SP pain with resistive adduction	Overhead sports and laborers Winged scapula and head in forward posture
	Lateral	Deltoid (D)	D pain with resistive abduction	
Elbow	Ventral	Long head of the biceps (LB)	LB pain with 10 degrees of resistive internal rotation	Worse if sleeping on the shoulder
	Medial	Subscapularis (SS)	SS pain on resistive internal rotation	Overhead throwers
	Lateral	Extensor carpi radialis brevis (ECRB)	ECRB pain on activities that require resisted wrist extension	Tennis or repetitive wrist extension
	Ventral	Biceps (B)	B Pain on elbow flexion and supination	Men with tobacco and anabolic steroid use
Wrist	Medial	Flexor carpi radialis (FCR)	FCR pain on resisted pronation and/or wrist flexion	Golf or repetitive wrist flexion
	Radial	EPL and APL (de quervain)	Pain on resisted radial deviation/extension of dig. 1	Hammering, cross country skiing, pregnancy
	Palmar	Finger flexor tendons (trigger finger)	Pain/nodule on the A1 pulley and triggering/locking of finger	Women with diabetes or RA
	Ulnar	Extensor carpi ulnaris (ECU)	ECU pain with gripping activities	More often in nonathletes
<b>Pain inLowerextremities</b>	<b>Pain location</b>	<b>Tendon</b>	<b>Diagnosis</b>	<b>Risk factors</b>
Hip	Lateral	Glutes medius (GM, trochanteric bursitis)	GM pain standing on one leg or sleeping on the side	Excessive hip adduction. Women >40 years
	Ventral	Iliopsoas (I)	I Pain and or clicking/snapping with hip flexion	Repetitive hip flexion
	Medial	Adductors (A)	Pain of a on resistive abduction	Sports as soccer, lumbar hyperlordosis
	Dorsal	Hamstring (H)	H Pain on terminal hip flexion or prolonged sitting	Runners, poor lumbo-pelvic control
Knee	Lateral	Iliotibial band (ITB)	ITB pain on leg horizontal and adducted. ITB popping.	Runners, friction of ITB on femoral condyle
	Ventral-distal	Patellar (PT)	Pain on proximal insertion of PT on the patella	Young athletes with jumping sports
	Ventral-proximal	Quadriceps (Q)	Pain on distal insertion of Q on the patella	Soccer, volleyball or running
	Medial-distal	Pes anserinus (PA)	Pain on PA 5–8 cm below knee joint on e.g., Climbing stairs	Runners, outer-rotation of lower leg
Ankle	Dorsal-lateral	Popliteus (PO)	PO pain on resisted knee flexion (15–30°) or internal rotation	Athletes with other knee ligament injuries
	Lateral	Peroneus (P)	P Pain on eversion and dorsiflexion	Feeling of ankle instability
	Ventral	Tibialis anterior (TA)	TA weakness with dorsiflexion	Runners >45 years
	Medial	Flexor hallucis longus (FHL)	FHL pain with resistive flexion of the great toe	Ballet dancers
	Medial	Tibialis posterior (TP)	TP pain with inversion and plantar flexion	Women >40 years
	Dorsal Plantar	Achilles tendon (AT) Plantar fascia (PF)	Mid-portion AT pain with plantar flexion Pain in the proximal PF by passive ankle/ first toe dorsiflexion	Running Obesity

The table depicts the upper- and lower extremity joints associated with the pain locations, risk factors and diagnostic tests that will render suspicion on one of the twenty-five most common tendons that are the origin of chronic pain.



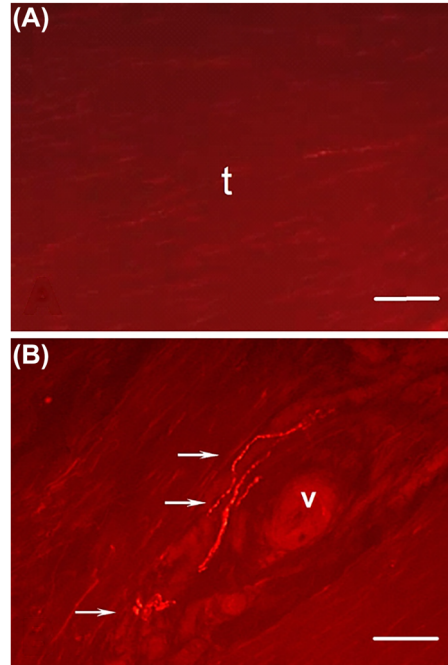
**Figure 1:** Microscopic anatomy (A-B).

Micrographs of tendon biopsies from a healthy, painfree individual (A) and from a patient with a chronic painful tendon (B). Hematoxylin and eosin staining demonstrate that the healthy patellar tendon has homogeneous, organized parallel collagen structure and thin, elongated tenocytes (A). In chronic painful tendinopathy, however, collagen disorganization, increased cell count, transformed tenocytes, and vascular ingrowth in the tendon proper are observed (B). Several studies, however, demonstrate no correlation between histological changes and pain [10, 14, 15] or between blood vessel ingrowth detected with power Doppler sonography or contrast-enhanced ultrasound and pain [14, 20–23]. Hematoxylin and eosin staining. Arrows denote tenocytes. Bar, 50  $\mu\text{m}$  (v=blood vessel). Reproduced with permission from Lian et al. 2006 [28].

correlated with tendon pain similarly as joint degeneration not is correlated with pain in osteoarthritis [18, 19].

### Does neovascularization correlate to tendon pain?

In the healthy tendon proper there are no visible blood vessels, but in tendinopathy blood vessels grow into the tendon proper (Figures 1, 2). Several studies, however, demonstrate no correlation between blood vessel ingrowth and increased flow detected with power Doppler sonography and pain or changes in function [14, 20–23]. To further confirm these data, contrast-enhanced ultrasound has been



**Figure 2:** Nerve ingrowth (A-B).

Immunofluorescence micrographs of Achilles tendon biopsies from a healthy, painfree individual (A) and from a patient with a chronic painful tendon (B). Immunostaining demonstrates that under (A) normal, healthy, conditions nerve fibers do not enter the tendon proper (intra-fascicular matrix). In painful tendinopathy (B) pathological ingrowth of sensory nerves is consistently observed in the intra-fascicular matrix. Nerve ingrowth has been demonstrated in different tendon pain locations such as Achilles tendinopathy [26, 27], patellar tendinopathy [28], rotator cuff tendinopathy [29], tennis elbow [30, 31] as well as in different painful tendon syndromes e.g., calcific tendinopathy [32], frozen shoulder [33].

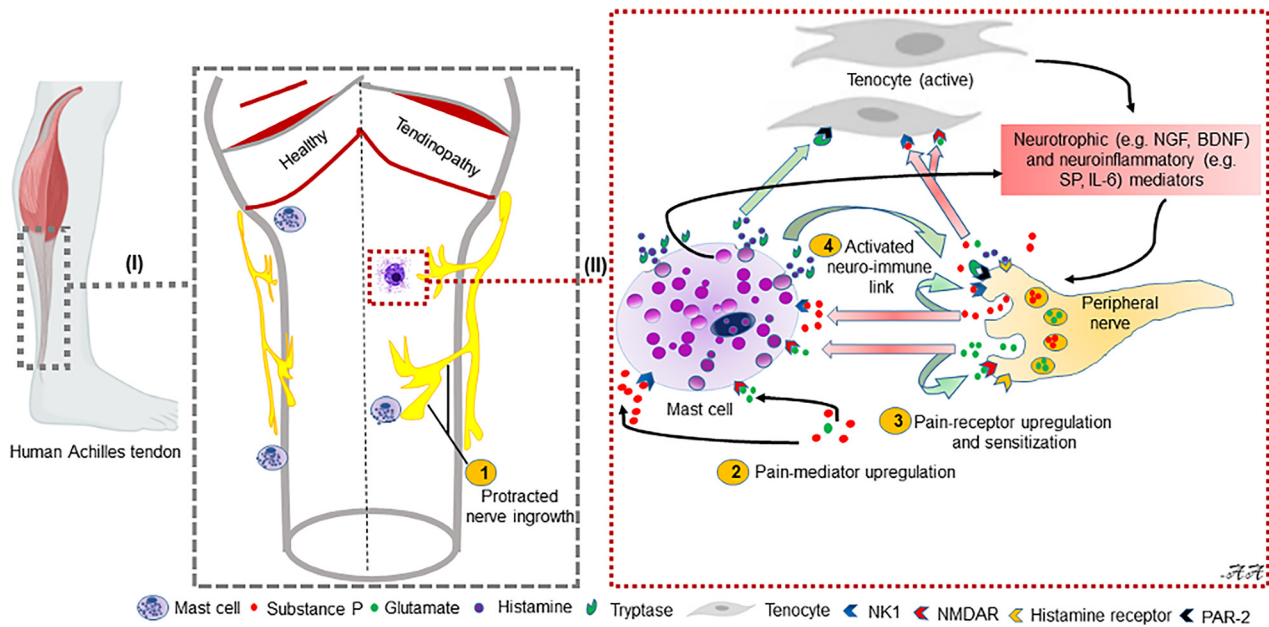
Immunostaining of sensory nerve fibers was performed using antibodies against the sensory neuropeptide, substance P. The picture is taken with immunofluorescence microscopy. Arrows denote free nerve endings (v=blood vessel). Bar=50  $\mu\text{m}$ .

Reproduced with permission from Ackermann et al. 2012 [81].

used, which found more abundant neovascularization in tendinopathy compared to non-contrast ultrasound. However, there was no correlation to symptoms of pain [14].

### Does tendon neuroanatomy correlate to tendon pain?

The nerve supply of intact healthy tendons is localized in the tendon sheath, whereas the tendon proper, i.e., intrafascicular matrix, is devoid of innervation (Figures 2, 3) [24]. This anatomical finding implicates that the tendon sheath is regulating acute episodes of tendon pain.



**Figure 3:** Schematic illustration of pathophysiology in chronic tendon pain.

In healthy tendons nerve fibers, blood vessels and inflammatory cells are confined to the tendon surrounding structures. Thus, acute inflammation and acute pain may occur in the tendon surrounding structures as paratendinitis, enthesitis etc. In response to e.g. repetitive mechanical stimuli peripheral nerve endings and tendon cells (tenocytes) [82] can release neurotrophic and neuroinflammatory mediators. Neurotrophic factors, such as nerve growth factor (NGF) [53] and brain-derived neurotrophic factor (BDNF), act trophically on nerve endings causing nerve sprouting with nerve fiber ingrowth into the tendon proper. Neuroinflammatory mediators, such as glutamate and substance P (SP), may activate the immune system (specifically mast cells) [83], tenocytes, and peripheral nerve endings via their respective receptors, i.e., glutamate receptors (e.g., NMDAR1) and NK1-receptors. Activated mast cells release proteases, e.g., tryptase, which may functionally impact tendon cells or activate nearby nerves. Mast cells also release NGF, which moreover stimulate upregulation of pain-receptors (e.g., NMDAR1) as well as pain mediators (e.g., SP, glutamate) on peripheral nerves. Activated tenocytes moreover drives production of neuro-inflammatory compounds (e.g., SP, NGF, IL-6). SP in turn may activate peripheral nerves (i.e., sensitization) via NK1 receptors in which NMDAR1 becomes activated (phospho-NMDAR1) and cause neurogenic inflammation [84, 85].

This figure was modified and adapted from Alim et al. 2020 [51]. NMDAR1, N-methyl-D-aspartate receptor type 1; NK1, neurokinin 1.

After tendon injury and during repair, extensive nerve ingrowth into the tendon proper has been found [24]. This nerve ingrowth was followed by a time-dependent expression of different neuronal mediators, which regulated healing pathways and nociceptive behaviour as demonstrated in a rat tendon healing model [25]. After tendon healing was completed, the nerve fibers retracted to the tendon envelope and nociception subsided [25].

In chronic painful tendons, excessive and protracted nerve sprouting with ingrowth in the tendon proper has been discovered (Figure 2) [24, 26–33]. This protracted nerve ingrowth exhibits a dysregulated expression of different mediators involved in pro-inflammatory, hypertrophic and nociceptive tissue responses (Table 2) (Figure 3) [34]. Among the sensory neuropeptides found upregulated in painful tendons, substance P (SP), has demonstrated effects on cell proliferation related to degenerative changes associated with tendinopathy, in

addition to pro-inflammatory and pain-triggering mechanisms (Figures 2, 4) [35–37].

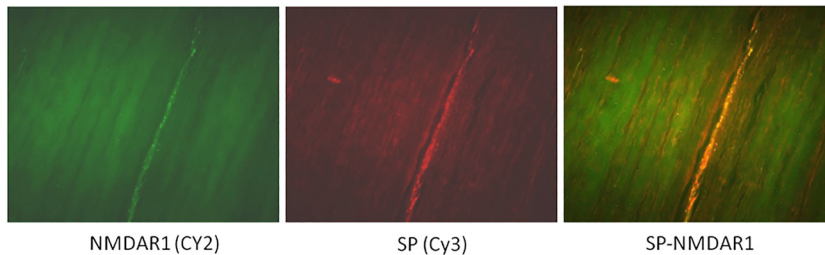
Tendons also exhibit autonomic- and glutamate signaling that may be involved in several persistent pain conditions. Accordingly, elevated levels of glutamate have been detected in patients with tendinopathy [38, 39] occurring in sprouting nerve fibers, which may represent glutamate involvement in nerve ingrowth and nociception [39–41].

Furthermore, painful tendons also exhibit upregulated expression of receptors for sensory, autonomic and excitatory mediators [24] (Table 2). The SP-receptor (neurokinin 1, NK1) was found up-regulated in painful tendons [42], and involved in up-regulation [40] and activation [43] of the excitatory glutamate receptor N-methyl-D-aspartate receptor 1 (NMDAR1), implicated in various pain disorders (Figure 4). Thus, in painful tendinopathy, a significant up-regulation of NMDA1 (9-fold) and of the activated receptor, Phospho-NMDAR (5-fold), has been found [39, 40].

**Table 2:** Neuromediator: receptor pathways in painful tendons.

Type	SUB-TYPE	Mediator	Receptor	Actions on nerve fibers <sup>n</sup>	Actions on immune system <sup>i</sup>
Sensory	Sensory	SP ↑ CGRP ↑	NK1 ↑ CRLR, RAMP-1	Sensitizing	Pro-inflammatory
	Opioid and opioid like	Enkephalins Cannabinoids Opioid like: GAL, SOM	δ-opioid receptor CB1 ↑ GalR1-3 <sup>a</sup> , SSTR1-5 <sup>a</sup>	Desensitizing	Anti-inflammatory
Autonomic	Sympathetic	Noradrenaline ↓ NPY	α-,β- adrenoceptors ↑ Y1 ↑	Desensitizing	Anti-inflammatory
	Para-sympathetic	Acetylcholine ↑ VIP	Muscarinic ↑ Nicotinic ↑ VPAC1-2 <sup>a</sup> , PAC1 <sup>a</sup>	Sensitizing Desensitizing	Pro-inflammatory Anti-inflammatory
Excitatory	Glutamatergic amino acid	Glutamate ↑	NMDA1 ↑ Phosfo-NMDA1 ↑ mGluR1 ↑ mGluR5 ↑ mGluR6-7 →	Sensitizing	Pro-inflammatory

The table describes the type and sub-type of mediators and receptors, which have been identified dysregulated in chronic painful tendons, and their actions on peripheral nerve fibers and immune cells. ↑, mediators/receptors that are upregulated in painful tendons; ↓, mediators/receptors that are downregulated in painful tendons; →, mediators/receptors that are equal amount in painful and non-painful tendons; SP, substance P; NK1, neurokinin 1; CGRP, calcitonin gene-related peptide; CRLR, calcitonin receptor-like receptor; RAMP-1, receptor activity-modifying protein 1; CB1, Cannabinoid receptor type 1; GAL, Galanin; SOM, Somatostatin; GALR1-3, Galanin receptor 1–3; SSTR1-5, Somatostatin receptor 1–5; NPY, Neuropeptide Y; VIP, Vasoactive intestinal peptide; VPAC1-2, Vasoactive intestinal peptide receptor 1–2; PAC1, Pituitary adenylate cyclase-activating peptidoreceptor; NMDA, N-methyl-D-aspartate receptor; mGluR, Metabotropic glutamate receptor. <sup>a</sup>Not yet assessed in tendon. <sup>n</sup>C-fibers and A-fibers. <sup>i</sup>The immune system includes a variety of cells, e.g., Mast cells. This figure was modified and adapted with permission from Ackermann et al. 2016 [24].

**Figure 4:** Pain receptor/mediator up-regulation (A-C).

Micrographs of tendon biopsies from a patient with a painful patellar tendinopathy (A-C). Immunostaining demonstrates expression of the pain receptor (A), N-methyl-D-aspartate receptor type 1 (NMDAR1), on the pathological ingrowth of sensory, substance P (SP) positive, nerves (B) seen in the intra-fascicular matrix. The yellow immunoreactivity shows co-existence of SP and NMDAR1 (C) displayed on the nerve fibers sprouting within the tendon proper. SP was shown to up-regulate NMDAR1 [40] and also to activate NMDAR1 by removing the magnesium block and thereby increasing the excitability of NMDAR1 [43]. Micrographs of longitudinal sections through patellar tendinopathy biopsies stained for NMDAR1 (Cy2 green; A) and SP (Cy 3 red; B) as well as double-stained NMDAR1-SP; NMDAR1-PGP 9.5 co-existence (yellow, merged) respectively. Bar, 50 μm (These figures are previously unpublished).

## Is there a neuro-inflammatory immuno connection in tendon pain?

One key effector cell in inflammation is the mast cell, which serves as an important link between the peripheral nervous system and the immune system [44–46]. These immune cells can be found in close proximity to peripheral nerve

endings and are one of the first to respond to sensory nerve activation [47, 48]. In support for a nerve-mast cell axis, the SP-receptor NK1 has been identified on mast cells [49].

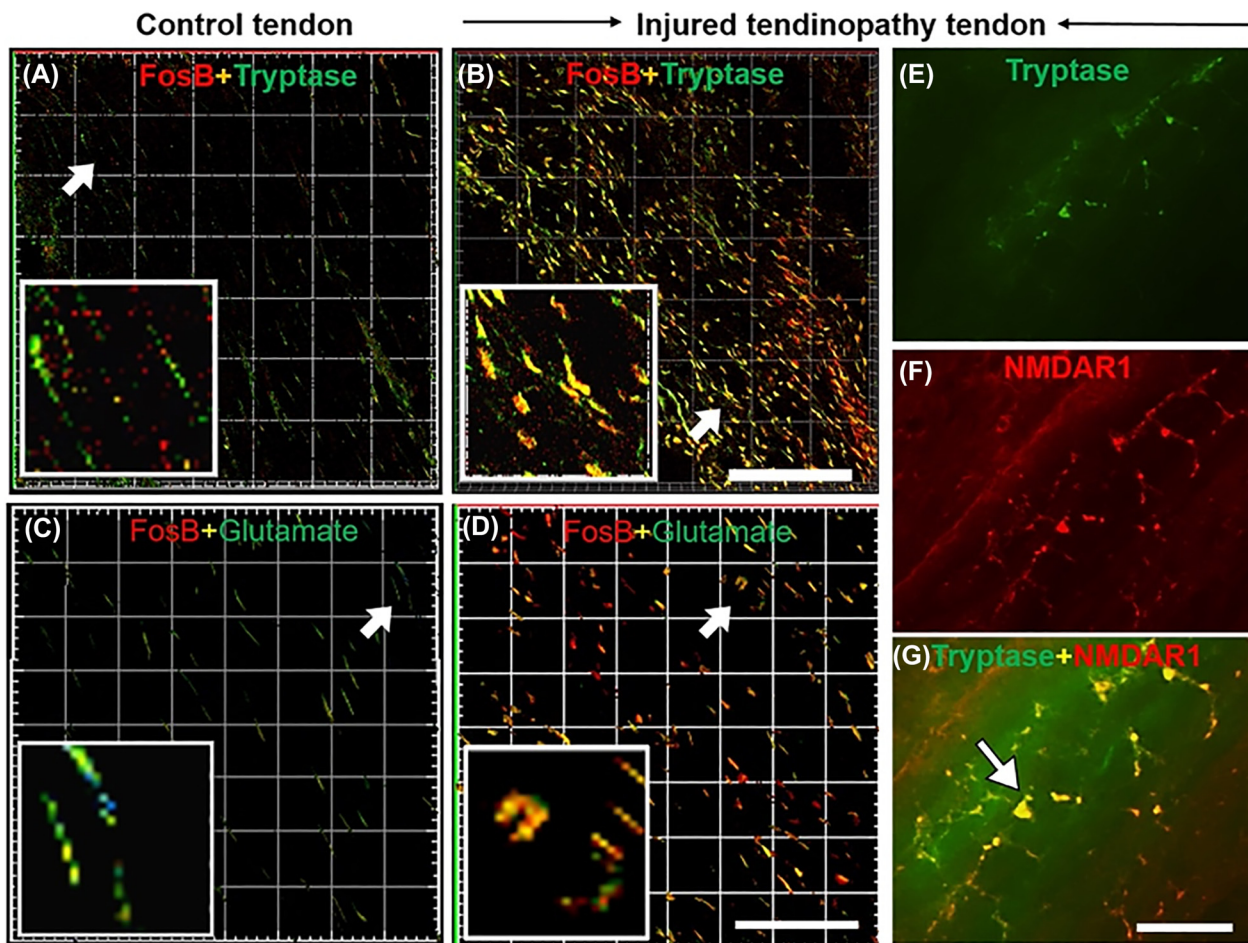
Recently it was demonstrated that glutamate also exhibits a signaling pathway to mast cells, when the expression of glutamate receptor on mast cells was

established by both *in-vivo* and *in-vitro* studies (Figure 5) [50, 51]. Exposure of mouse mast cells to glutamate activates a transient expression of a range of glutamate receptors [51], and also resulted in an increased level of pro-inflammatory cytokines/chemokines, introducing the concept of a glutamate-glutamate receptor axis in mast cells, which can contribute to neurogenic inflammation and pain regulation in the tendon. Glutamate stimulation of mast cells resulted in upregulated expression of a number of transcription factors, in particular FosB (Figure 5) [51], which is implicated in pain regulation. Altogether, glutamate signaling and its various receptor involvement may evolve as a potential pathogenic mechanism operative in tendon pain [52].

## Discussion

This topical review found no correlations between radiological and histological tissue alterations including neovascularization and chronic tendon pain. Substantial evidence, however, was found suggesting that chronic painful tendons exhibit (1) protracted ingrowth of sensory nerves (2) elevated pain mediator levels and (3) up-regulated expression and excitability of pain receptors, which participate in a (4) neuro-immune pathways involved in pain regulation.

Sensory nerve sprouting, regulated by NGF [53], with ingrowth into pathologic tendons seem to represent an important pain mechanism. Interestingly, this pain



**Figure 5:** Neuro-immune connection with transcriptional factor in the control and injured tendinopathy tendon (A-G). Immunofluorescence image showing increased colocalization of FosB and MC tryptase (Mcp6) in the painful injured Achilles tendon (B) compared to the control tendon (A). Immunofluorescence images showing colocalization of FosB and glutamate in the control (C) and painful injured tendon (D). Note the abundance of cells double positive for FosB and glutamate in the injured tendinopathy, but not in the control tendon. In the right panel (E-G), MC tryptase (E, green) and glutamate receptor NMDAR1 (F, red) are colocalized (G, yellow) in the injured tendinopathy tissue. Scale bars: 100  $\mu\text{m}$ . Reproduced with permission from Alim et al. 2017, 2020 [50, 86].

mechanism seem generalized since other painful dense connective tissue disorders exhibit similar pathophysiology, with nerve ingrowth into normally aneuronal tissue. Thus, in chronic low back pain, sensory nerve ingrowth into the normally non-innervated intervertebral disc has likewise been identified as a pain-generating mechanism [54]. Also in unspecific muscular low back pain conditions as well as pain conditions of the fascia, nerve ingrowth has been observed in normally aneuronal rat fascia tissue [55].

Other tissues that lack sensory innervation during normal conditions include healthy articular cartilage, subchondral bone marrow and meniscus. Accordingly, ingrowth of nerve fibers into these tissues has been established, and such nerve ingrowth has been suggested as a potential origin of pain in osteoarthritis [56–58]. Nerve ingrowth into synovial joint tissue was furthermore regulated by NGF and it was shown that anti-NGF treatment decreased both nerve ingrowth and pain-related behavior in a mouse model [58].

Sensory nerve ingrowth into normally aneuronal tendon tissue has the potential to generate nociception in response to mechanical, thermal or chemical stimuli. Thus, many patients experience pain only on mechanical activation, i.e., exercise, of their tendons. In the progression of the disease, patients may additionally feel a lingering pain after the exercise is finished, indicating a sensitization of nociceptors. The patients' differential experience of pain may thus be explained by alterations of both the amount of nociceptive mediators and nociceptors as well as sensitization of the peripheral and central nervous system [9, 59].

Current treatments of chronic tendon pain, which entail the highest scientific evidence, include eccentric exercises, i.e., muscle lengthening exercises under load, and extracorporeal shockwave therapy (ESWT), i.e., non-invasive acoustic shock waves leading to reinjury/regeneration of bone or soft tissue [1, 60]. Intriguingly, these treatments are both locally applied and target the peripheral nervous system, which seems to strengthen the conception of protracted neoinnervation as a driver of tendon pain.

Eccentric exercise has been called “probably the greatest single advance in the management of tendinopathy in the past 20 years” and many rehabilitation programs have been developed for different tendons [61, 62]. An interesting notion regarding eccentric exercise is that it has been demonstrated to stimulate synthesis of different neurotrophic substances such as NGF and BDNF both in muscles and tendons [42, 63–65]. Activation of neurotrophic pathways is related to survival and neuroregeneration of peripheral neurons [63, 64].

Whether eccentric exercise specifically can modulate nerve ingrowth, release of nociceptive mediators and up-regulation of peripheral nociceptors is mostly unknown. Eccentric exercise has, however, been demonstrated to activate the peripheral nervous system with release of neuropeptides [66], to modulate nerve plasticity, retraction and regeneration during healing [67] after injury [63, 64].

ESWT has recently been demonstrated to be efficient both as single therapy as well as in combination with eccentric exercise in chronic tendon pain [60, 68–70]. Interestingly, the most important effect of ESWT has been demonstrated to affect the peripheral nervous system by selective denervation of sensory, unmyelinated nerve fibers [71]. These data suggest a specific mechanism to target the pain mechanism in tendon, namely nerve ingrowth.

Given the identification of protracted nerve ingrowth as a predominant mechanism underlying chronic tendon pain, the question arises if drug therapies could be developed by targeting promoters and inhibitors of nerve ingrowth? Promoters of nerve ingrowth that have been identified include e.g. NGF and BDNF, while inhibitors of nerve ingrowth include semaphorins [72] and neuropilins [73].

NGF inhibitors in the form of anti-NGF monoclonal antibodies, are already present as hot drug candidates used in clinical trials and are projected to become the emerging treatment option for chronic pain conditions. Importantly, blockade of NGF will target all pain mechanisms shown in tendons by inhibition of NGF-stimulated: (1) nerve ingrowth, (2) synthesis of nociceptive mediators, (3) nociceptor transport and (4) mast cell degranulation. However, such NGF inhibitors have been on hold by the FDA in US due to development of osteoarthritis [74–77]. The mechanisms for developing osteoarthritis with anti-NGF are not fully explored, but may include excessive wear and tear in the absence of joint pain or/and that anti-NGF blocks pathways involved in neuronal regulation of tissue homeostasis [75, 77]. Thus, anti-NGF therapy has not yet been tested for chronic tendon pain.

Since anti-NGF therapy seems associated with certain side-effects, perhaps a more targeted blocking of nociceptive mediator-receptor pathways could have an ameliorating impact on pain without pronounced side-effects? One of the most prominent pathways in chronic tendon pain is that of the SP:NK1 axis, where both the mediator and receptor are up-regulated. The concept that NK1 receptor blockers would represent a novel class of analgesic drugs, as suggested by the preclinical studies, has however not been confirmed by the clinical trials that have been reported thus far [78].



Glutamate signaling arises as the second pathway with a potential pathogenic mechanism operative in chronic tendinopathy. Strategies to target both glutamate and its receptor, which both are upregulated in tendinopathy, could thereby represent potential therapeutic options in tendon pain disorders. NMDAR is the glutamate receptor that has been highlighted in a multitude of chronic pain conditions [79, 80]. There are several potent NMDA-receptor antagonists available, e.g. Ketamine, however most are associated with side effects in the central nervous system. Ways to overcome these side-effects could include more specific drug-targets for the peripheral nervous system, which could be locally administered. Ketamine has positive local effects when applied peripherally in low doses and should be further studied when it comes to tendinopathy.

Targeting the NMDA receptor with specific antagonists could, in addition to having direct effects on nociceptive transmission in nerves, affect the NMDA receptor on mast cells and thereby hinder the degranulation-dependent release of sensitizing substances [50, 51]. However, further studies are required to fully understand how the inhibition of glutamate signaling and/or mast cells can affect tendon pain.

The mechanisms presented in this article provides a basis for a mechanism-based treatment approach where pharmacological treatments could be developed by targeting promoters of nerve ingrowth such as NGF and BDNF as well as inhibitors of nerve ingrowth like semaphorins and neuropilins. Possible pharmacological treatment targets are also the SP:NK1 or the glutamate-NMDA-receptor pathways, both of which are prominent in chronic tendon pain.

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**Competing interests:** Authors state no conflict of interest.

**Informed consent:** Informed consent was obtained from all individuals included in this study.

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