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Scoping Review

Chronic Tendinopathy Driven by Neoinnervation: The Role of the Paratenon, Upregulated Neural Biomarkers, and Evolving Evidence – A Scoping Review

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Background: This scoping review systematically evaluates and synthesizes evidence on the presence of neoinnervation in chronic tendon pain. By analyzing the frequency and progression of neural biomarker upregulation, the present investigation seeks to illuminate existing knowledge gaps, contextualize shifts in research focus over time, and propose potential therapeutic approaches for the more precise and effective management of tendinopathy.

Objectives: To identify major neural biomarkers associated with nerve ingrowth, detailing historical development, current understanding, and implications in tendinopathy.

Study Design: A scoping review.

Setting: An academic medical center.

Methods: Searches were conducted up to June 2024 using PubMed, Embase, Web of Science, and Scopus, adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines. The selected studies included clinical human case-control studies and in vivo experimental animal models that examined neoinnervation in tendinopathy. Data extraction included study design, animal induction models, biomarker detection methods, neural biomarker upregulation, and supporting evidence to evaluate the involvement of neoinnervation and the role of the paratenon in tendinopathy.

Results: Of the 26 studies reviewed, 19 (73%) identified neoinnervation in chronic tendinopathy, and 20 (76.9%) highlighted the role of the paratenon, suggesting its potential as a key target for therapeutic interventions. Notably, 14 studies (53.8%) examined both neoinnervation and the paratenon's role, indicating significant interplay. Analyses of neural biomarkers revealed possible upregulation of protein gene product 9.5 (PGP 9.5) in 15 studies (57.6%) and substance P in 13 studies (50%), emphasizing the crucial roles of those biomarkers in the neurobiological mechanisms of tendinopathy pain. Other biomarkers, including calcitonin gene-related peptide (CGRP), tyrosine hydroxylase, growth-associated protein-43 (GAP-43), NMDA receptor (NMDAR), glutamate, neurokinin 1 receptor (NK1R), neuropeptide Y, adrenoreceptor, nerve sprouting markers, specific chemokines, and various immune-related markers, were also identified as potentially upregulated. Our review of temporal trends indicates that recent research has expanded to encompass a broader range of biomarkers, thereby enhancing our understanding of the complexity and multisystem involvement in the pathology of tendinopathy.

Limitations: This review is limited by the predominance of case-control and experimental studies, which inherently offer lower levels of evidence due to methodological constraints like lack of randomization and potential biases. Additionally, the present review may not fully address how biomarker expression or neoinnervation changes over disease stages or treatment, the comprehension of which is critical for understanding progression and management.

Conclusion: The present investigation highlights the critical role of neoinnervation and the

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paratenon in chronic tendinopathy, with a significant overlap suggesting interrelated roles in the condition. This finding emphasizes the need to incorporate neurobiological pathways into therapeutic strategies. The evolution of neural biomarker studies reveals a complex interplay in pain mechanisms, underscoring the potential for targeting specific nerve ingrowth pathways within the paratenon to enhance treatment efficacy. Future research should aim to elucidate the therapeutic potential of targeting specific paratenon nerve ingrowth pathways, which could improve the efficacy of treatments for chronic tendon pain substantially.

Key words: nerve tissue proteins, receptors, immunology, peritendinous tissue, paratenon, nerve sprouting, tendinopathy, tendon pain

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Tendinopathy is characterized by structural or cellular abnormalities in tendon tissue (1). Traditionally regarded as a result of mechanical overload and degenerative changes, tendinopathy is understood as an imbalance between tendon damage and repair, with a focus on the pathophysiology of the condition (2-4). However, recent advances have expanded our understanding of tendinopathy significantly, revealing that neurobiological factors, particularly neoinnervation or nerve ingrowth from paratendinous tissues or paratenon, play a crucial role in its pathophysiology. The paratenon is a thin, vascularized connective tissue layer surrounding the tendon, facilitating gliding motion and serving as a site for neoinnervation and nociceptive signaling in tendinopathy (5-8). This shift underscores the importance of neurobiological mechanisms in both understanding and managing tendinopathy.

The concept of neoinnervation involves the sprouting of new nerve fibers from the paratenon into the fibrous layers of damaged tendons. Neoinnervation is the process of new nerve fiber growth and sprouting in response to tissue injury, associated with pain modulation and inflammatory responses in chronic tendinopathy. Excessive and protracted neoinnervation, observed as the characteristic of chronic tendon pain, is increasingly recognized as a major regulator of pain and symptom chronicity in tendinopathy (6,9-11). The presence of nociceptors such as substance P and glutamate, associated with nerve growth, may exacerbate or perpetuate pain, suggesting that neoinnervation could be a critical target for therapeutic intervention (12-15). Despite this progress, the variability in study methodologies and outcomes has led to gaps in our comprehensive understanding of the role and effects of neoinnervation. This scoping review aims to systematically evaluate and synthesize evidence on neoinnervation within chronic tendon pain contexts. By examining the progression and current understanding of major neural biomarkers and their upregulation, this review seeks to explain the complex interactions between neural activities and tendinopathy. We explore shifts in research focus over time, address existing knowledge gaps, and discuss the implications of these findings for developing targeted treatment strategies. This critical analysis not only clarifies the dynamic involvement of neural pathways in tendinopathy but also enhances strategies for managing this challenging condition effectively, offering insights into potential therapeutic targets and fostering advancements in clinical practices.

Methods

The present investigation was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines as outlined in the 2018 explanatory paper (16). The PRISMA-ScR 2018 checklist was followed to ensure comprehensive coverage of the design, analysis, and reporting stages.

Search Strategies

Systematic searches were conducted across PubMed, Embase, Web of Science, and Scopus databases from their inception until June 2024. The search included the following terms: ("Tendinopathy" OR tendino* OR tendonitis OR tendinitis OR "chronic tendon pain") AND (nerve ingrow* OR neuronal ingrow* OR neural ingrow* OR neur* ingrow* OR neoinnervation OR neoinnerv* OR nerve sprout* OR neural sprout* OR neuronal sprout*). The review also involved screening reference lists from the full-text articles retrieved to identify any additional relevant studies that might have been missed initially.

Inclusion and Exclusion Criteria

The inclusion criteria encompassed various types of research, including clinical case-control studies, in vitro studies, and animal studies that examined tendons for the analysis or investigation of neoinnervation in chronic painful tendons or tendinopathy. The exclusion criteria included review articles, case reports, and studies not published in English.

Study Selection and Data Extraction

The study selection process was conducted by 4 independent reviewers. Any discrepancies were resolved through consensus or, if necessary, by consulting a fifth expert reviewer who provided the decisive judgment when consensus could not be achieved. The data extraction encompassed study design, specimen collection methods, study models, detection techniques, sample sizes, the phase and site of tendinopathy, and the status of neural biomarkers or neuropeptides, categorized as "upregulated," "not upregulated," or "unclear due to conflicting evidence." Additionally, critical hypotheses and supporting evidence were assessed to evaluate the role of neoinnervation and the paratenon in tendinopathy.

Results

Search Yield

The comprehensive search across 4 databases, along with additional reference tracking, initially yielded 208 records. After the removal of 89 duplicates, 119 research articles were screened for titles and abstracts. This process led to the assessment of the full text of 47 records, from which 26 studies met the criteria and were included in this scoping review. The final set of studies spanned from 2001 to 2022. Further details are presented in Fig. 1 (17). This study adhered to the PRISMA-ScR 2018 Checklist, as detailed in the Appendix.

Study Characteristics

Human Studies

Twenty-one human studies conducted between 2001 and 2022 involved 462 patients, who had a total of 479 tendons affected by chronic tendinopathy. These studies focused on the patella tendon (8 studies), Achilles tendon (7 studies), rotator cuff (3 studies), biceps tendon (2 studies), and other tendons, including the extensor carpi radialis bravis, greater trochanteric bursa, and gluteal tendons (7,8,11,15,18-34). Further details are summarized in Supplementary Table 1. Methodologically, 17 of the studies adopted a case-control design, while 4 did not incorporate control groups. Sample sizes ranged from 6 to 63 patients, whose conditions persisted beyond 3 months (meaning they had reached the chronic stage). Predominantly, the research utilized immunohistochemistry and immunofluorescence techniques for detecting specific markers on living biopsy samples (Table 1).

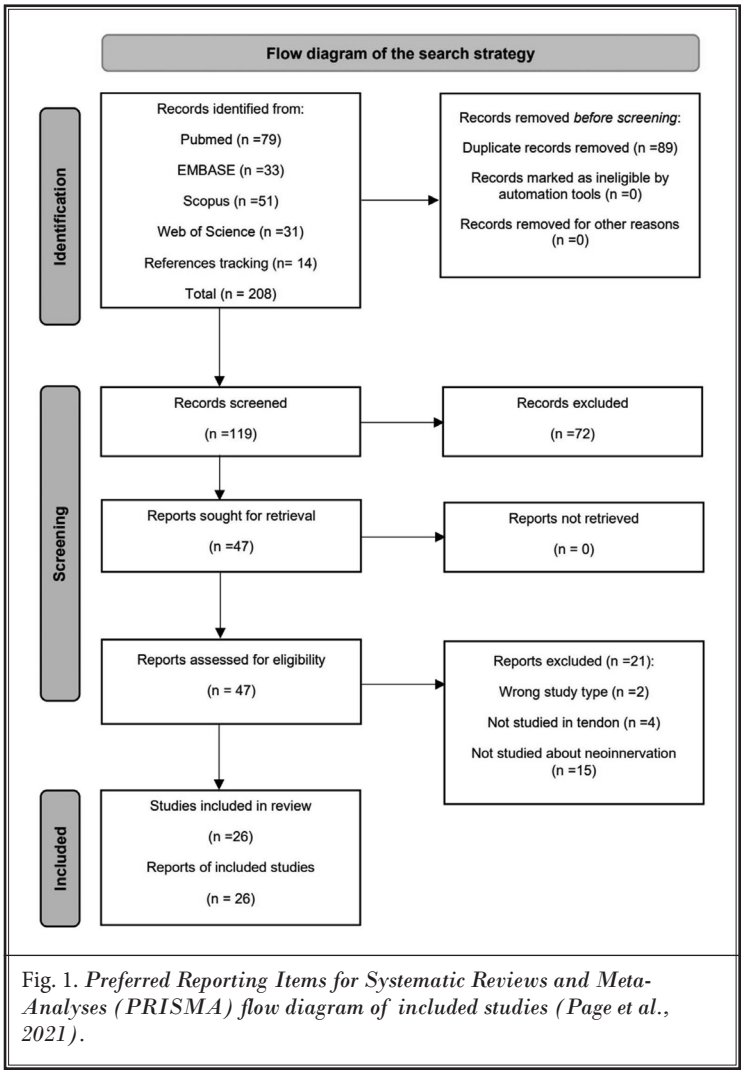


Fig. 1. *Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of included studies (Page et al., 2021).*

Table 1. *Type and detection methods of human studies.*

Authors	Year	Study Type	Specimen	Tendon Site	Detection Method
Spang et al. (7)	2022	Case series	Scraped from living patient	Patella tendon	IMH
Blumer et al. (31)	2020	Case control	Living biopsies	Biceps tendon	IF
Spang and Alfredson (33)	2017	Case series	Living biopsies	ECRB tendon	IMH, IF
Hackett et al. (8)	2016	Case control	Living biopsies	Rotator cuff tendon	IMH, IF
Christensen et al. (27)	2015	Case control	Living biopsies	Achilles tendon	IF
Fearon et al. (34)	2014	Case control	Living biopsies	Greater trochanteric bursa, gluteal tendon	IMH
Xu et al. (29)	2012	Case control	Living biopsies	Rotator cuff capsule	IMH, IF, H&E
Schizas et al. (15)	2012	Case control	Living biopsies	Patella tendon	IMH
Xu et al. (30)	2011	Case control	Living biopsies	Supraspinatus tendon	IMH, H&E
Schizas et al. (23)	2010	Case control	Living biopsies	Patella tendon	IF
Andersson et al. (25)	2008	Case control	Living biopsies	Achilles tendon	IF, ISH
Scott et al. (18)	2008	Case control	Living biopsies	Patella, Achilles tendon	IF, ISH
Singaraju et al. (32)	2008	Case control	Living biopsies	Biceps tendon	IMH
Danielson et al. (22)	2007	Case control	Living biopsies	Patella	IF
Andersson et al. (28)	2007	Case series	Living biopsies	Achilles	IF
Lian et al. (20)	2006	Case control	Living biopsies	Patella	IMH, IF
Schubert et al. (11)	2005	Case control	Living biopsies	Achilles	IMH, IF
Bjur et al. (26)	2005	Case control	Living biopsies	Achilles	IMH
Alfredson et al. (24)	2003	Case control	Living biopsies	Achilles	IMH
Alfredson et al. (19)	2001	Case control	Living biopsies	Patella	Microdialysis, IMH
Sanchis -Alfonso et al. (21)	2001	Case series	Living biopsies	Patella	IMH, H&E

Abbreviations: ECRB, extensor carpi radialis brevis; NR, no reported; IMH, immunohistochemistry; IF, immunofluorescence; H&E, hematoxylin-eosin stain; ISH, in situ hybridization

Animal Studies and Induction Model

Five animal studies conducted between 2002 and 2018 utilized rats and mice to investigate the effects and recovery processes of induced Achilles tendon ruptures, serving as models for human tendinopathy (35-39). These studies, which involved a total of 308 animals, employed in vivo experimental approaches with post-mortem tissue collection to analyze the tendon at various stages. Tissue samples from the ventral, middle, and dorsal sections—primarily the middle and full thickness of the Achilles tendon—were subjected to comprehensive analyses using detection techniques such as immunohistochemistry, immunofluorescence, and hematoxylin and eosin staining. Each study utilized specific methodologies to induce tendon injuries for the experiments. Mechanical induction was a common technique for mimicking tendinopathy across all studies, with 4 studies employing blunt instruments to rupture the tendon (36-39). One of those studies took the unique approach of supplementing mechanical rupturing with chemical interventions, applying agents such as substance P, thiorphan, and captopril directly to the injury sites to explore the therapeutic effects of said agents on tendon healing (37). Another study standardized the injury model by using sharp surgical blades to create complete lacerations in mice (35). The experimental design included both control and experimental groups, with animal numbers ranging from 5 to 40. In a particularly comprehensive study conducted by Steyaert et al (37), 3 distinct experimental groups and one control group were all subjected to identical mechanical injuries followed by varied treatments to assess the latter's effects on tendon repair and recovery. Observation periods across the studies varied from one day to 16 weeks after the interventions. This extensive observation captured major processes such as inflammation, cellular migration, nerve ingrowth, and tissue remodeling. As for sample sizes and specific interventions, Stålman et al and Ackermann et al each included 40 animals in their respective experimental and control groups, whereas the other studies utilized a total of 47 animals with a notably smaller control group of 5

Table 2. *Model of animal studies.*

Authors	Year	Type of Study	Species	Tendinopathy Model	Tendon Site	Tissue Site	Detection method
Xu et al. (35)	2018	In vivo	Mice	Surgical blade used for complete laceration	Achilles tendon	Mid-portion	IF
Stålman et al. (36)	2015	In vivo	Rats	Blunt instrument used for tearing fibers apart	Achilles tendon	0.5 cm above the calcaneal insertion	IMH, IF
Steyaert et al. (37)	2010	In vivo	Rats	Blunt instrument used to rupture fibers	Achilles tendon	Mid-portion	IF, H&E
Ackermann et al. (38)	2003	In vivo	Mice	Blunt instrument used for tearing fibers apart	Achilles tendon	Mid-portion	IMH, IF, H&E
Ackermann et al. (39)	2002	In vivo	Rats	Blunt instrument for tearing fibers apart	Achilles tendon	Ventral, middle, and dorsal side	IMH, IF

Abbreviations: NR, no reported; IMH, immunohistochemistry; IF, immunofluorescence; H&E, hematoxylin-eosin stain

animals (36,38,39). Steyaert et al consistently involved 24 animals per group, integrating pharmacological treatments to evaluate their effectiveness in modulating the healing responses (37). The characteristics of animal studies are presented in Supplementary Table 2, and the details of the animal model are summarized in Table 2.

Role of the Paratenon in Tendinopathy

The paratenon is a crucial structure in chronic tendinopathy, with 76.9% of studies (20 out of 26) highlighting its role in mediating nociception and regulating pain (7,15,19,20,22-28,30,32-39). This tissue serves as an active site for nociceptive and regenerative processes, particularly in the early post-injury phase. Immunoreactivity to neuronal markers such as NMDAR1 and substance P in the paratenon suggests its involvement in early nerve-mediated responses (15,19,23,39). Additionally, evidence shows that peritendinous RFP-labeled cells migrate to wound sites, supporting tissue regeneration and cellular regulation (35). Fourteen studies (53.8%) reported significant overlap between neoinnervation and paratenon function, emphasizing the combined role of the phenomena in tendinopathy mechanisms. This interplay underscores the importance of these processes in understanding tendinopathy pathology and guiding treatment strategies. However, 6 studies (23%) did not address the paratenon's role, suggesting research gaps and the need for more uniform study designs (Supplementary Table 3).

Evidence of Neoinnervation in Tendinopathy

Neoinnervation was identified in 73% of studies (19 out of 26), confirming its contribution to the progression of tendinopathy (7,8,11,15,20-26,29-31,33,35,36,38,39). Biomarkers such as substance P were linked consistently to nerve ingrowth and pain, highlighting their active roles from injury onset through recovery and emphasizing their potential as therapeutic targets (11,15,36). These studies further suggest that together, nerve proliferation, alongside angiogenesis, synergistically promotes tendon healing (8,24). While most studies support the role of nerve ingrowth in tendinopathy, variability exists. One study challenged the consensus, reporting no significant association between nerve ingrowth and tendinopathy symptoms (37). Despite this disagreement, the overall evidence strongly supports the importance of neoinnervation and its interactions with vascular changes in the pathology of tendinopathy (Supplementary Table 3).

Upregulation of Neural Biomarkers Associated with Neoinnervation in Tendinopathy

Neural biomarkers provide critical insights into the mechanisms of nerve ingrowth and inflammation in tendinopathy. The most frequently reported marker, PGP 9.5, was upregulated in 15 studies spanning animal and human case-control designs (8,15,20,22-24,26,28-31,33,36,37,39). Substance P, identified in 13 studies, plays a key role in pain and inflammatory modulation, while CGRP was reported in 9 studies, further supporting its involvement in nociception. Tyrosine hydroxylase was found to be upregulated in 6 studies, emphasizing its significant role in sympathetic innervation and catecholamine synthesis, which is linked closely to pain pathways. In one study, however, tyrosine hydroxylase was reported as not upregulated. GAP-43, known for its involvement in new nerve growth and nerve regeneration, was upregulated in 3 studies. NMDA receptors (NMDAR1) were upregulated in 3 human case-control studies, as was glutamate, while the neurokinin 1 re-

ceptor (NK1R) was also upregulated in 3 studies. This upregulation highlights the potential roles of these receptors in the neurochemical processes associated with tendinopathy. Adrenoreceptors were reported as upregulated in 2 human case-control studies, one of which identified the alpha-1 subtype. Neuropeptide Y was upregulated in 2 studies, while galanin, associated with pain and inflammation modulation, was upregulated in one study. Markers for nerve sprouting, such as beta tubulin reaction and S-100, were identified in studies. Additional cellular and molecular markers identified include RFP-labeled cells, PARs receptors, macrophages (CD68 and CD206), T cells (CD3), mast cells (mast cell tryptase), vascular endothelium (CD34), and specific chemokines such as CCL5, CCL2, CCL3 and CXCL10. These findings indicate more complex pathways involved in the pathology of tendinopathy that extend beyond nerve ingrowth (Fig. 2, Table 3).

Trends in Neural Biomarker Research

This scoping review highlights 2 decades of neural biomarker research in tendinopathy, revealing shifts in the focus and diversity of studied markers (Fig. 3). Studies in the first decade of the twenty-first century focused on PGP 9.5 and substance P, sparking interest in and laying the groundwork for understanding neural contributions to nociception and pain in tendinopathy. During this period, interest among researchers expanded to include CGRP and NMDAR, reflecting broader exploration of pain pathways and signaling mechanisms. Peaks in research activity around 2007 and 2010, particularly for substance P and CGRP, likely correlated with seminal studies that influenced subsequent work. Meanwhile, emerging biomarkers such as NMDAR and NK1R exhibit variable reporting frequencies, indicating evolving hypotheses regarding their roles in tendinopathy.

From 2010 to 2020, investigations into substance P, CGRP, and NMDAR intensified, underscoring their roles in neurogenic inflammation and pain modulation. New markers such as tyrosine hydroxylase, neuropeptide Y, GAP-43, and B-tubulin emerged, broadening research into autonomic innervation and nerve regeneration mechanisms.

After 2020, focus on established markers like PGP 9.5, substance P, and NMDAR continued, with increasing attention to cellular mechanisms. A plateau or decline in reports during this period suggests a shift toward novel research areas or a matured understanding of these biomarkers. Recent studies integrate advanced molecular techniques and highlight inflammatory and immune markers, including chemokines, macrophages

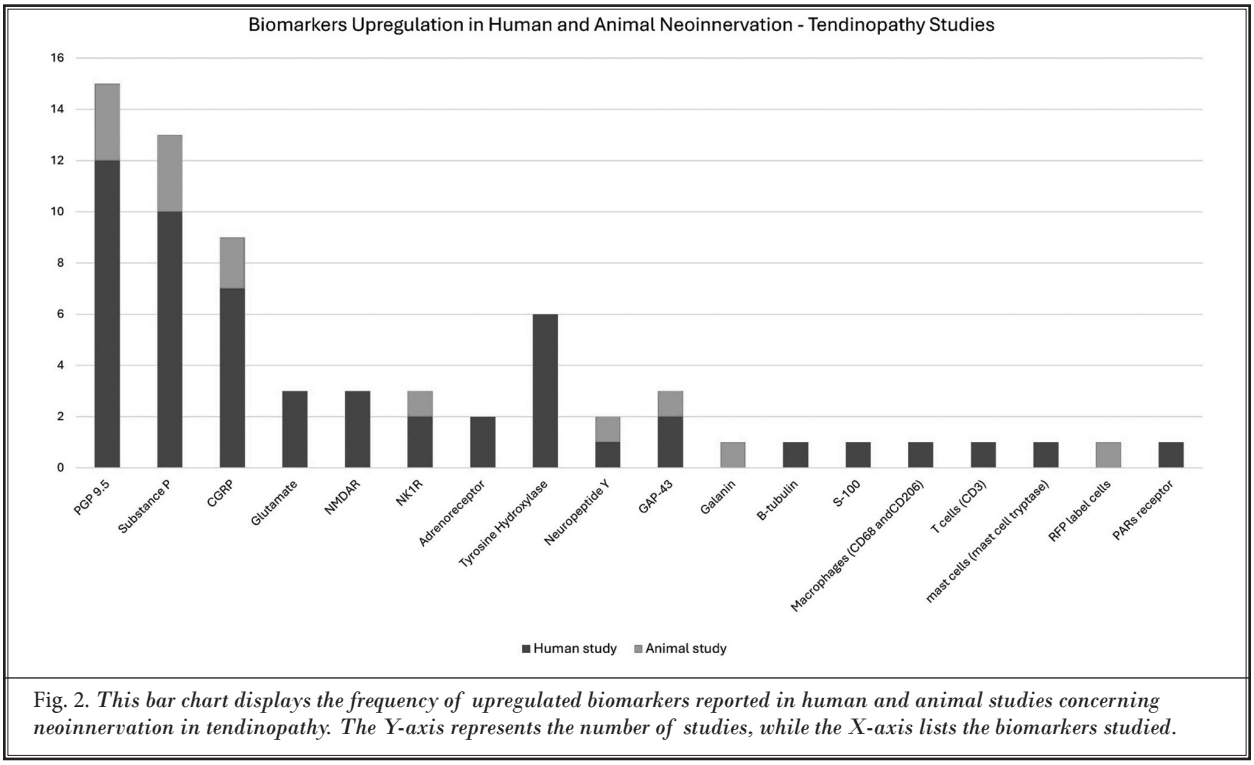
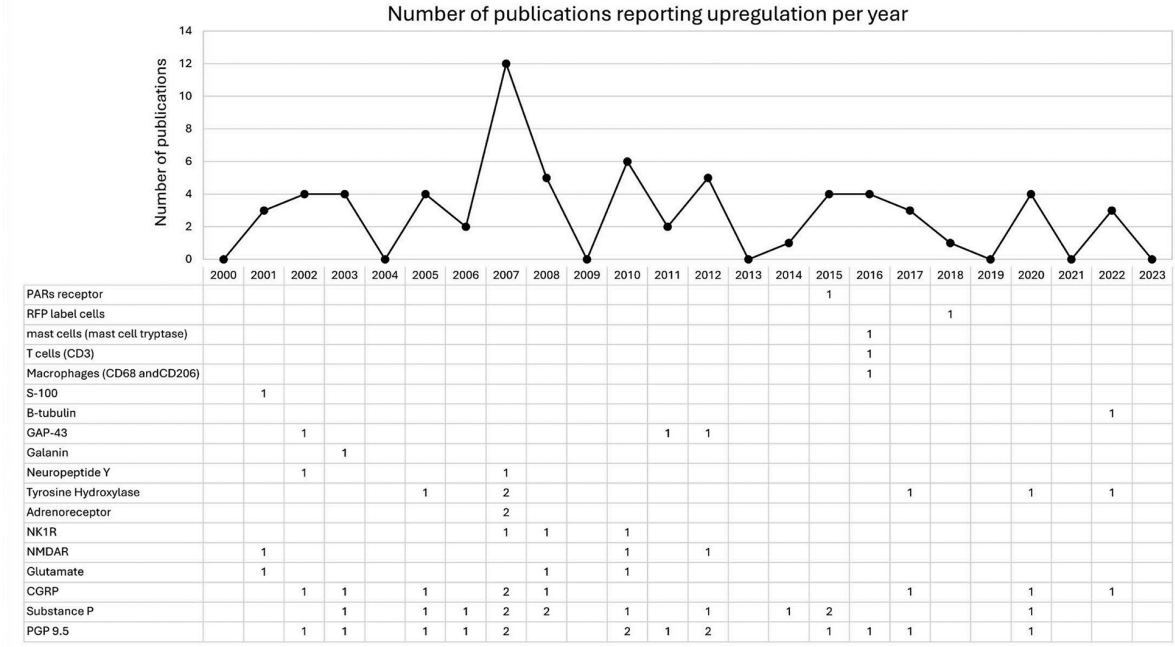


Fig. 2. *This bar chart displays the frequency of upregulated biomarkers reported in human and animal studies concerning neoinnervation in tendinopathy. The Y-axis represents the number of studies, while the X-axis lists the biomarkers studied.*

Table 3. *Summary of biomarkers findings in each study.*

Authors	Year	PGP9.5	SP	CGRP	Glutamate	NMDAR	NK1R	Adreno-receptor	Tyrosine hydroxy-lase	Neuro-peptide Y	Others
Spang et al. (7)	2022			/					/		B-tubulin
Blumer et al. (31)	2020	/	/	/					/		GAP-43
Xu et al. (35)	2018										RFP-labelled cells
Spang and Alfredson (33)	2017	/		/					/		
Hackett et al. (8)	2016	/									CD68, CD206, CD3, CD34, mast cell tryptase
Stålman et al. (36)	2015	/	/								CCL5, CCL2, CCL3, CXCL10
Christensen et al. (27)	2015		/								PARs receptor
Fearon et al. (34)	2014		/								
Xu et al. (29)	2012	/									GAP-43
Schizas et al. (15)	2012	/	/			/					
Xu et al. (30)	2011	/									GAP-43
Steyaert et al. (37)	2010	/	/				/				
Schizas et al. (23)	2010	/			/	/					
Andersson et al. (25)	2008		/				/				
Scott et al. (18)	2008				/						
Singaraju et al. (32)	2008		/	/							
Danielson et al. (22)	2007	/	/	/				/	/	/	
Andersson et al. (28)	2007	/	/	/			/	/	/		
Lian et al. (20)	2006	/	/						×		
Schubert et al. (11)	2005								/		
Bjur D et al. (26)	2005	/	/	/							
Ackermann et al. (38)	2003		/	/							Galanin
Alfredson et al. (24)	2003	/									
Ackermann et al. (39)	2002	/		/						/	GAP-43
Alfredson et al. (19)	2001				/	/					
Sanchis-Alfonso et al. (21)	2001										S-100



	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
PARs receptor																1								
RFP label cells																			1					
mast cells (mast cell tryptase)																	1							
T cells (CD3)																	1							
Macrophages (CD68 andCD206)																	1							
S-100		1																						
B-tubulin																							1	
GAP-43			1									1	1											
Galanin				1																				
Neuropeptide Y			1					1																
Tyrosine Hydroxylase						1		2										1			1		1	
Adrenoreceptor								2																
NK1R								1	1		1													
NMDAR		1									1		1											
Glutamate		1							1		1													
CGRP			1	1		1		2	1									1			1		1	
Substance P				1		1	1	2	2		1		1		1	2					1			
PGP 9.5			1	1		1	1	2			2	1	2			1	1	1			1			

Fig. 3. *This chart displays the evolution of research interest in various neuromarkers across different time periods.*

(CD68, CD206), T cells (CD3), and mast cell tryptase, illustrating the interplay of neurogenic, inflammatory, and immune responses in tendinopathy. Unique markers such as RFP-labeled cells and PARs receptors represent innovative approaches to studying cellular behaviors in tendinopathic tissues.

Discussion

The present investigation advances the understanding of chronic tendinopathy through a neurological pathway lens, elucidating the roles of neoinnervation and the paratenon, identifying upregulated neural biomarkers, and examining biomarker research trends over time. Integrating findings from 21 human studies and 5 animal models, this review highlights substantial interactions between experimental and clinical research. The paratenon is shown to play a significant role in mediating nociception and regulating pain, an observation supported by 20 of 26 studies. Beyond exhibiting post-injury reactivity, the paratenon contributes actively to healing through nerve regeneration and cellular regulation (28,35). Mechanisms such as the role of substance P in inflammation and the regenerative phase further underline the importance of the paratenon (20,37). The confirmation of nerve growth and inflammatory markers in the paratenon adds to the growing body of evidence suggesting a neuroinflammatory component in tendon pain and dysfunction (30,40,41). Evidence from 19 studies underscores the importance of neoinnervation in neurobiological pathways and its correlation with pain and neurogenic inflammation. However, methodological variations necessitate further clarification of neoinnervation's exact role in the pathology of tendinopathy (9,42).

Neural biomarkers, including PGP 9.5, substance P, and CGRP, are upregulated prominently, highlighting their roles in chronic tendon pain. PGP 9.5 serves primarily as a biomarker for visualizing tendon innervation patterns, with potential utility in diagnostics or research but limited therapeutic application (43). Substance P and CGRP exhibit a directly actionable profile as nociceptive neuropeptides. Upregulated in sensory nerves during tendinopathy, they play dual roles by promoting tissue healing through vasodilation and angiogenesis while also contributing to tendon damage via neurogenic inflammation, apoptosis, and prolonged exposure (2,14,19,42,44,45). Although substance P has shown therapeutic promise in some contexts, such as enhancing early-stage healing after Achilles tendon repair, the variability in the effects of this neuropeptide highlights the need for further investigation (46). Targeting the SP-NK1R axis could offer novel pain management strategies, though clinical trials are required to confirm their efficacy and safety

(6,47,48). Autonomic biomarkers, such as tyrosine hydroxylase (TH) and neuropeptide Y (NPY), have gained attention as indicators of sympathetic nerve activity. Their presence suggests that dysregulated autonomic innervation may contribute to persistent pain and the impaired healing of tendons (22). GAP-43, associated with nerve regeneration and new nerve growth, underscores nerve sprouting as a key mechanism linked to chronic tendon pain (49). Additionally, contemporary research increasingly highlights NMDAR, cytokines, and immune markers, such as mast cell tryptase, macrophages, and T-cell receptors, emphasizing the neuro-immune pathway's role in chronic tendon pain development and persistence (50-53).

The shift in research focus over the decades reflects a deeper understanding of the neurobiology of tendinopathy. Although early studies primarily characterized nerve presence using PGP 9.5, later research explored nociceptive neuropeptides (SP, CGRP), neuro-immune mechanisms (chemokines, cytokines, and mast cells), and neurotransmitter receptors (NMDAR, NK1R). This evolution signifies a paradigm shift from merely identifying nerve ingrowth to elucidating how neural and immune interactions contribute to pain chronicity and tendon degeneration.

Temporal trends suggest a growing focus on diverse biomarkers, reflecting an evolving understanding of neuro-inflammatory mechanisms in tendinopathy. Future research should integrate these findings to unravel the complex interplay of neurogenic and immune-regulated pathways, potentially enabling more targeted and effective therapies. Personalized approaches based on specific biomarker profiles and disease stages could further optimize treatment outcomes.

The present review also identifies gaps in existing research. The predominance of cross-sectional studies provides only a static view of tendinopathy. Longitudinal studies are needed to track the progression of neoinnervation and paratenon changes, revealing their dynamic roles in chronic pain and healing. Moreover, novel therapeutic targets remain underexplored. Although therapies targeting neoinnervation and paratenon disruption show promise, experimental validation and clinical efficacy remain under-researched. More studies are needed to evaluate the effectiveness of these interventions as therapeutic mechanisms for both pain relief and tendon healing. Further investigation should explore larger-scale clinical trials and the cost-effectiveness of interventions to improve treatment accessibility.

Limitations

A limitation of the present investigation is that most of the included studies are case-control and experimental in nature. These designs typically provide a lower level of evidence due to inherent methodological constraints, such as the lack of randomization and potential biases. While these limitations are understandable given the feasibility and specific outcomes of interest, the findings should be interpreted with caution. There is a need for more robust, high-quality research, including randomized controlled trials, to strengthen the evidence base for the role of neoinnervation and related interventions in chronic tendinopathy. Furthermore, the review may not fully capture how changes in biomarker expression or neoinnervation evolve over stages of disease or in response to treatment, which is crucial for understanding disease progression and management. Future research should address these temporal aspects and further refine the understanding of these mechanisms.

Conclusion

Integrating these findings into therapeutic strategies offers promising avenues for enhancing treatment efficacy. Targeting neural components within the paratenon may provide effective pain relief while supporting tendon repair. The denervation of the paratenon may be the common denominator of the treatments reviewed here (54). In this regard, an ultrasonic approach to the paratenon should also be considered to treat chronic tendinopathic pain, by a focal neurolysis of the paratenon nociceptors (10,55,56). Minimally invasive stripping, focused on paratenon separation, aims to directly target and disrupt the nerve ingrowth mechanism (57,58). Sclerosing injections with polidocanol and high-volume image-guided injections (HVIGI) are designed to eradicate neovessels and associated nerve fibers, which may also be a future treatment strategy (59-61). While these treatments hold significant promise for managing chronic tendinopathy, their complications have been reported, and each has its limitations (57,62). Notably, current payment models in the United States do not cover treatments involving paratenon modifications. However, research on paratenon modification is promising, suggesting that the technique may be a viable option for chronic tendinopathic pain. Currently, in the United States, the only reimbursed percutaneous procedure that involves separating the paratenon and has shown good outcomes with minimal adverse

events is percutaneous ultrasound tenotomy using TENEX® (10,55,56,63). Future research should investigate how this intervention impacts the paratenon and neuronal mechanisms in tendinopathy to validate that intervention's effectiveness and potential therapeutic benefits.

Supplemental material is available at www.painphysicianjournal.com

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Supplementary Table 1. *Characteristics of human studies*.

Authors	Year	Group	Tendon Status	Tendon Sample Size (Patients)	Phase of Disease
Spang et al. (7)	2022	Case (painful patella tendinopathy)	Tendinopathy	6	Chronic
		No control group	-	-	
Blumer et al. (31)	2020	Case (long head of biceps tendon from patients with OA shoulder or head split fracture that cannot be reconstructed)	NR	11 (6 OA shoulder + 5 head split fracture)	Chronic
		Control (human spinal cord from an organ donor for positive antigen control)	NA	NA	
Spang and Alfredson (33)	2017	Case (tennis elbow)	Tendinopathy	9 (7)	Chronic
		No control group	-	-	
Hackett et al. (8)	2016	Case 1 (suprascapularis calcific tendinitis)	Tendinopathy	10	Chronic
		Case 2 (rotator cuff tear)	Tendinopathy	10	
		Control (patients treated with stabilization for subscapularis tendon)	No tendinopathy	10	
Christensen et al. (27)	2015	Case (Achilles tendinosis surgery)	Tendinopathy	17	Chronic
		Control (healthy individuals)	No tendinopathy	4	
Fearon et al. (34)	2014	Case (gluteal tendon reconstructive surgery and bursectomy)	Severe tendinopathy	34	Chronic
Schizas et al. (15)	2012	Case (jumper's knee)	Tendinopathy	10	Chronic
		Control (tibial shaft fractures undergoing intramedullary nailing)	No tendinopathy	8	
Xu et al. (29)	2012	Case (frozen shoulder)	Tendinopathy	8	Chronic
		Control (rotator cuff tear but no stiffness)	Tendinopathy	10	
Xu et al. (30)	2011	Case (supraspinatus tendon, rotator cuff tear)	Tendinopathy	26	NR
		Control (subscapularis tendon in instability shoulder but no sign of tendinopathy)	No tendinopathy	10	
Schizas et al. (23)	2010	Case (jumper's knee)	Tendinopathy	10	Chronic
		Control (tibia fractures—intramedullary nailing without current or previous knee pain)	No tendinopathy	8	
Andersson et al. (25)	2008	Case (chronic painful mid-portion Achilles tendinosis; IF)	Tendinopathy	20	Chronic
		Control (healthy Achilles tendon; IF)	No tendinopathy	7	
		Case (chronic painful mid-portion Achilles tendinosis; ISH)	Tendinopathy	9	
		Control (healthy Achilles tendon; ISH)	No tendinopathy	3	
Scott et al. (18)	2008	Case (patellar tendinopathy + Achilles tendinopathy)	Tendinopathy	14 (one patella) + (13 Achilles)	Chronic
		Control (healthy, pain-free patella + Achilles tendon)	No tendinopathy	15 (one patella) + (7 Achilles)	
Singaraju et al. (32)	2008	Case (arthroscopic-assisted biceps tenodesis)	Tendinopathy and tenosynovitis	6	Chronic
		Control (healthy cadavers)	No tendinopathy and tenosynovitis	6	
Andersson et al. (28)	2007	Case (painful mid-portion Achilles tendinosis)	Tendinopathy	15	Chronic
		No control group	-	-	
Danielson et al. (22)	2007	Case (chronic painful patella tendinosis)	Tendinopathy	7	Chronic
		Control (pain-free patella tendon)	No tendinopathy	15	
Lian et al. (20)	2006	Case (jumper's knee)	Tendinopathy	10	Chronic
		Control (healthy individuals)	No tendinopathy	10	

Supplementary Table 1 cont. *Characteristics of human studies*.

Authors	Year	Group	Tendon Status	Tendon Sample Size (Patients)	Phase of Disease
Bjur D et al. (26)	2005	Case (chronic painful mid-portion Achilles tendinosis)	Tendinopathy	21	Chronic
		Control (healthy individuals)	No tendinopathy	9	
Schubert et al. (11)	2005	Case (painful Achilles tendinosis)	Tendinopathy	10	Chronic
		Control (spontaneously ruptured tendon without previously pain)	Ruptured tendon	10	
Alfredson et al. (24)	2003	Case (painful Achilles tendinosis)	Tendinopathy	25 (24)	Chronic
		Control (healthy individuals)	No tendinopathy	20 (14)	
Alfredson et al. (19)	2001	Case (painful jumper's knee—patella tendon)	Tendinopathy	5	Chronic (12-36 months)
		Control (healthy individuals)	No tendinopathy	5	
Sanchis-Alfonso et al. (21)	2001	Case (patellar tendon from jumper's knee)	Tendinopathy	17	Chronic (13 months)
		No control group	-	-	
		Control (total hip arthroplasty)	Mild tendinopathy	29	

Supplementary Table 2. *Characteristics of animal studies*.

Authors	Year	Group	Tendon Status	Sample Size	Duration After Induced Model
Xu et al. (35)	2018	Experiment (induced Achilles tendon rupture)	Induced tendon rupture	NR	After modeling and tendon rupture at one, 2, 3, 4 weeks
		No control group	-	-	
Stalman et al. (36)	2015	Experiment (induced Achilles tendon rupture)	Induced tendon rupture	40	After tendon rupture with one day, 3 days, and one, 2, 4, 6, 8, 12, 16 weeks after surgery
		Control (intact healthy Achilles tendon)	Intact tendon	40	
Steyaert et al. (37)	2010	Experiment One (induced Achilles tendon rupture with paratenon injection of SP 10-6 µmol/kg BW combined with thiorphan and captopril)	Induced tendon rupture	24	After paratenon injection at 2, 3, 4, 5, 6 days
		Experiment 2 (induced Achilles tendon rupture with paratenon injection of SP 10-8 µmol/kg BW combined with thiorphan and captopril)	Induced tendon rupture	24	
		Experiment 3 (induced Achilles tendon rupture with paratenon injection of thiorphan and captopril)	Induced tendon rupture	24	
		Control (induced Achilles tendon rupture with paratenon injection of normal saline)	Induced tendon rupture	24	
Ackermann et al. (38)	2003	Experiment (induced Achilles tendon rupture)	Induced tendon rupture	47 (35 for IMH + 12 for nociceptive test)	After modeling and tendon rupture at one, 2, 4, 6, 12, 18, 16 weeks
		Control (intact healthy Achilles tendon)	Intact tendon	5	
Ackermann et al. (39)	2002	Experiment (induced Achilles tendon rupture)	Induced tendon rupture	40	After modeling and tendon rupture at one, 2, 4, 6, 8, 12, 16 weeks
		Control (contralateral intact Achilles tendon)	Intact tendon	40	

Abbreviations: NR, no reported; SP, substance P; IMH, immunohistochemistry

Supplementary Table 3. *Summary of results among key findings on neoinnervation and the role of the paratenon in tendinopathy.*

Authors	Year	Reference to Neoinnervation in Tendinopathy	Summary of Findings on Neoinnervation in Tendinopathy	Reference to the Paratenon Role in Tendinopathy	Summary of Findings on the Role of the Paratenon in Tendinopathy
Spang et al. (7)	2022	Mentioned	In patients with patellar tendinopathy, neoinnervation or sprouting nerve fibers were observed originating from the peritendinous tissue. Supporting this observation, all tissue specimens exhibited high levels of blood vessels and nerves—including fascicles, sprouting nerve fibers, and perivascular innervation—as evidenced by hematoxylin and eosin (H&E) staining.	Mentioned	In a subgroup of patients with patellar tendinopathy, who exhibited severe tenderness in the proximal patellar tendon, marked innervation appeared in the superficial peritendinous tissue. These findings suggest that this tissue may serve as an additional pain driver in certain individuals.
Blumer et al. (31)	2020	Mentioned	GAP43 innervation suggests neoinnervation in the long head of the biceps tendon (LHBT). Both myelinated and unmyelinated axons in this region exhibit molecular features indicative of nociceptive nerve fibers. Moreover, a distinct subpopulation of unmyelinated axons presents molecular characteristics typical of sympathetic nerve fibers. These unmyelinated sympathetic and nociceptive fibers express proteins typically associated with developmental and regenerative phases. The present findings support the hypothesis that the ingrowth of nociceptive fibers plays a crucial role in chronic tendon pain.	Not mentioned	Not mentioned
Xu et al. (35)	2018	Mentioned	Early nerve ingrowth is essential for the regeneration of the Achilles tendon following injury. This ingrowth is facilitated by neural crest-derived cells, which migrate into the injured site and are critical in promoting angiogenesis. These processes are mediated by the interaction between nerve tissues and newly formed blood vessels. The nerve ingrowth is closely associated with the presence of neural crest-derived cells, indicating their pivotal role in the tendon's healing process.	Mentioned	Neural crest-derived cells, tracked using Sox10-Cre/ROSA26-Flox-RFP transgenic mice, migrate from nerves into the peritendinous tissue of the Achilles tendon during healing. These cells express markers indicative of their roles in nerve and vascular regeneration, supporting their involvement in angiogenesis and tendon repair. This phenomenon demonstrates the critical role of peritendinous tissue in coordinating nerve ingrowth and vascularization, essential for effective tendon regeneration.
Spang and Alfredson (33)	2017	Mentioned	The study highlights the significance of early nerve regeneration, emphasizing the ingrowth of nerve fibers into the tendon proper as crucial for tendon healing. It mentions the expression of PGP 9.5, tracking nerve ingrowth. Additionally, during the regenerative phase, sprouting nerve fibers were observed near newly formed blood vessels, suggesting a link between vascularization and nerve ingrowth in the healing process.	Mentioned	The study found rich innervation in the peritendinous tissues, which includes both sympathetic and sensory nerve fibers. Immunohistochemical analysis for general nerve markers like protein gene product 9.5 (PGP 9.5), as well as markers for sympathetic (tyrosine hydroxylase, TH) and sensory nerve fibers (calcitonin gene-related peptide, CGRP), confirmed the presence of these nerve types in the peritendinous tissues.
Hackett et al. (8)	2016	Mentioned	Neovascularization was positively correlated with more frequent pain experiences. In the calcific tendinitis group, there was a two- to eightfold increase in nerve markers, neovascularization, macrophages, M2 macrophages, and mast cells compared to both the rotator cuff group and the control group. These findings suggest a connection between inflammatory mediators and peripheral nervous and vascular cells, contributing to the pathogenesis and potentially the pain associated with calcific lesions.	Not mentioned	Not mentioned

Supplementary Table 3 cont. *Summary of results among key findings on neoinnervation and the role of the paratenon in tendinopathy.*

Authors	Year	Reference to Neoinnervation in Tendinopathy	Summary of Findings on Neoinnervation in Tendinopathy	Reference to the Paratenon Role in Tendinopathy	Summary of Findings on the Role of the Paratenon in Tendinopathy
Stalman et al. (36)	2015	Mentioned	All analyzed chemokines were detected in every Achilles tendon sample. The study discusses early nerve regeneration and the successive ingrowth of nerve fibers into the tendon proper, highlighting their essential role in tendon healing. This process is characterized by the expression of PGP 9.5, a general nerve marker, and involves the activation of chemokines and sensory neuropeptides such as substance P (SP), which facilitate the healing process.	Mentioned	Nerve fibers immunopositive to PGP and SP are mainly observed in the paratenon and surrounding loose connective tissue during the remodeling phase, 8 weeks post-rupture. This indicates the role of the paratenon in the healing process and its relationship with nerve regeneration and inflammation.
Christensen et al. (27)	2015	Not mentioned	Not mentioned	Mentioned	The findings revealed that protease-activated receptors (PARs) are distributed within the tendon proper and paratendinous tissue, with expression on both nerves and vascular structures. Double staining demonstrated co-localization of PARs with nociceptive fibers that expressed substance P.
Fearon et al. (34)	2014	Not mentioned	Not mentioned	Mentioned	There was a significantly greater presence of substance P (SP) in the bursa, but not in the tendon, of patients with greater trochanteric pain syndrome (GTPS) than in patients within the control group. This increased presence of SP in the trochanteric bursa may be associated with the pain symptoms observed in GTPS.
Xu et al. (39)	2012	Mentioned	This study suggests that neoinnervation and neoangiogenesis within the shoulder capsule play significant roles in the pathogenesis of frozen shoulder. These processes may contribute to explaining the often severe pain experienced by patients with this condition.	Not mentioned	Not mentioned
Schizas et al. (15)	2012	Mentioned	Co-localization of substance P (SP) and phosphorylated NMDA receptor 1 (phospho-NMDAR1) within the tendon proper is unique to tendinopathic conditions. This co-localization was observed on hypertrophic tenocytes, blood vessels, and free nerve fibers penetrating the tendon. Additionally, sprouting nerve fibers in the tendon proper were confirmed by positive PGP 9.5 staining. In-depth analysis revealed SP presence on these sprouting nerve fibers in half of the biopsies from male patients showing late-stage tendinosis signs. None of the control biopsies displayed SP-positive nerve fibers within the tendon. The specific localization of SP and phospho-NMDAR1 on altered tenocytes and sprouting nerve endings highlights the pathological changes in the tendon architecture associated with tendinopathy.	Mentioned	Elevated immunoreactivity for substance P (SP) and phosphorylated NMDA receptor 1 (phospho-NMDAR1) in tendinopathic biopsies occurs both in the peritendinous loose connective tissue and within the tendon proper. Phospho-NMDAR1 positive free-nerve fibers were specifically noted in the peritendinous loose connective tissue. Contrastingly, in both the paratenon and loose connective tissue, co-localization of SP and phospho-NMDAR1 was observed in tendinopathy and control samples alike, predominantly in nerve bundles, nerve endings, and cells. This finding suggests a broader distribution of these markers in nerve-related structures regardless of tendinopathy status, with specific elevation and localization differences in tendinopathic conditions.

Supplementary Table 3 cont. *Summary of results among key findings on neoinnervation and the role of the paratenon in tendinopathy.*

Authors	Year	Reference to Neoinnervation in Tendinopathy	Summary of Findings on Neoinnervation in Tendinopathy	Reference to the Paratenon Role in Tendinopathy	Summary of Findings on the Role of the Paratenon in Tendinopathy
Xu et al. (30)	2011	Mentioned	In normal tendons, markers PGP9.5 and GAP43 are found primarily in the paratendinous tissue, but in tendinopathy, their presence increases significantly within both the paratendinous tissue and the tendon proper, especially near hypercellular areas. Similarly, CD34-positive vessels, typically limited to the paratendinous connective tissues and endotenon in healthy tendons, appear in the tendon proper in tendinopathic tendons. This marked increase in nerve and vascular markers suggests active neoinnervation and is indicative of the pathological changes in tendinopathy, potentially exacerbating pain and other related symptoms.	Mentioned	In normal tendons, nerve fibers and CD34-positive vessels marked by PGP9.5 and GAP43 are located mainly in the paratendinous tissue and endotenon. In tendinopathy, however, there is a significant increase in these markers within both the paratendinous tissue and the tendon proper. This phenomenon suggests that the paratenon plays a crucial role in the pathophysiology of tendinopathy, potentially influencing its progression and severity through involvement in inflammatory and pain responses.
Steyaert et al. (37)	2010	Contrast Mentioned	The study found that despite the administration of substance P, no nerve ingrowth was observed in sutured rat Achilles tendons. While substance P enhanced endogenous levels promoting fibroblast proliferation, it did not stimulate sensory nerve ingrowth, suggesting its effects in tendon healing may not extend to nerve regeneration in this model.	Mentioned	The study notes that during the early inflammatory phase, SP-positive nerve fibers were expressed predominantly in the loose connective tissue around tendons. By the regenerative phase, SP presence was mainly noted in the paratenon, indicating its role in the tendon's inflammatory and healing processes.
Schizas et al. (23)	2010	Mentioned	The study discusses the occurrence of nerve fibers marked by PGP9.5, indicating nerve regeneration or sprouting, which co-localize with increased levels of NMDAR1 and glutamate in tendinopathic tendons but not in control samples. This suggests active neoinnervation and nerve sprouting in the pathological process of tendinopathy, likely contributing to pain and other symptoms.	Mentioned	In tendinopathic samples, increased NMDAR1 immunostaining was observed in the loose connective tissue around the tendon proper. Double staining revealed glutamate presence in nerve bundles and vessel walls within this tissue, and in free nerve endings in the tendon proper. The study highlights the paratenon as crucial during tendon healing, especially in the remodeling phase, where chemokine expression shifts from the tendon proper to the paratenon. This shift, along with the retraction of nerve fibers to the paratenon, suggests its key role in regulating inflammation and nerve dynamics during tendon recovery.
Andersson et al. (25)	2008	Mentioned	The presence of sprouting SP-positive nerve fibers in the Achilles tendon affected by tendinosis. This sprouting is considered part of the pathological changes associated with tendinopathy and may contribute to pain and other symptoms observed in the condition. The presence of SP mRNA and its receptor NK-1 in tenocytes, suggesting that SP might play a role in nerve sprouting and the broader pathophysiology of tendinopathy.	Mentioned	The paratendinous tissue is vital for nerve fibers and blood vessels, where increased activity of SP and its receptor NK-1 is observed in tendinopathic tendons. This suggests that the paratendinous tissue may contribute significantly to the pain and inflammatory responses in tendinopathy, potentially influencing the progression of the condition through its role in nerve sprouting and the local production of neuropeptides.
Scott et al. (18)	2008	Not mentioned	Not mentioned	Not mentioned	Not mentioned

Supplementary Table 3 cont. *Summary of results among key findings on neoinnervation and the role of the paratenon in tendinopathy.*

Authors	Year	Reference to Neoinnervation in Tendinopathy	Summary of Findings on Neoinnervation in Tendinopathy	Reference to the Paratenon Role in Tendinopathy	Summary of Findings on the Role of the Paratenon in Tendinopathy
Singaraju et al. (32)	2008	Not mentioned	Not mentioned	Mentioned	The interaction between the biceps tendon and its surrounding soft tissues, including the tendon sheath, plays a significant role in the etiology of anterior shoulder pain. The study highlights that increased vascularity and inflammation in the tendon sheath may contribute to the pain.
Danielson et al. (22)	2007	Mentioned	Sympathetic and sensory innervation is found primarily around the blood vessels in the loose paratendinous connective tissue, with very few nerve fibers present in the tendon proper under normal conditions. In tendinosis, however, there is increased immunoreactivity for adrenergic receptors and tyrosine hydroxylase (TH) within the tendon proper. These findings suggest that the paratendinous tissue serves as a source of innervation, and there is evidence of neuronal ingrowth from the paratendinous tissue into the tendon proper, which is associated with the pathology of tendinosis.	Mentioned	In normal conditions, sympathetic and sensory innervation is found predominantly around blood vessels in the paratendinous tissue and is scarce in the tendon proper. However, in tendinosis, immunoreactivity for adrenoreceptors and TH is observed within the tendon proper. These findings suggest that the paratendinous tissue is a source of tendon innervation, with neuronal ingrowth from the paratendinous tissue into the tendon proper being associated with tendinosis.
Andersson et al. (28)	2007	Not mentioned	Primarily, this study discusses the presence of sensory and sympathetic nerve fibers within the paratendinous tissue and their association with pain in chronic Achilles tendinosis. The study focuses on the existing nerve supply rather than detailing any neoinnervation.	Mentioned	The study highlights the presence of both sensory and sympathetic nerve fibers, as well as increased nerve fascicles in the paratendinous tissue, suggesting significant nerve involvement in the pain mechanisms of chronic tendinosis.
Lian et al. (20)	2006	Mentioned	The study notes the occurrence of sprouting SP-positive nonvascular sensory nerve fibers in chronic painful tendons. This nerve ingrowth within the tendon proper is linked to the pathophysiology of tendinopathy and may contribute to the associated pain.	Mentioned	The classic vessel-related proinflammatory actions of SP may take place in the tendon envelope, specifically within the paratenon and loose connective tissue.
Schubert et al. (11)	2005	Mentioned	Painful Achilles tendinosis is associated with the presence of SP-positive nerve fibers, which may contribute to the clinical pain. The condition likely results from repeated microtrauma, leading to tissue reorganization and the sprouting of nociceptive SP-positive nerve fibers.	Not mentioned	Not mentioned
Bjur D et al. (26)	2005	Mentioned	In tendinopathic tendons, there is an increase in the presence of these nerve fibers not only in the paratendinous tissue but also within the tendon proper. Nerve fibers in tendinopathic tendons are more commonly found associated with fine blood vessels within the tendon. This phenomenon can be interpreted as evidence of nerve ingrowth from the paratendinous tissue into the tendon proper.	Mentioned	The study shows that in both normal and tendinopathic Achilles tendons, nerve fibers are present in the paratendinous loose connective tissue. However, in tendinopathic tendons, there is an increased presence of nerve fibers, especially those marked by PGP9.5 and CGRP/SP, within the tendon proper. This observation suggests that the paratendinous tissue serves as a source of these nerve fibers, which may invade the tendon proper during the progression of tendinopathy.

Supplementary Table 3 cont. *Summary of results among key findings on neoinnervation and the role of the paratenon in tendinopathy.*

Authors	Year	Reference to Neoinnervation in Tendinopathy	Summary of Findings on Neoinnervation in Tendinopathy	Reference to the Paratenon Role in Tendinopathy	Summary of Findings on the Role of the Paratenon in Tendinopathy
Ackermann et al. (38)	2003	Mentioned	After the rupture of the Achilles tendon, which normally lacks nerve fibers, there is extensive new nerve ingrowth into the tendon proper during the early phase of healing. This nerve ingrowth is associated with the presence of sensory neuropeptides such as SP and calcitonin gene-related peptide (CGRP). The findings suggest that this ingrowth of nerve fibers, which includes sprouting of SP and CGRP-positive fibers, plays a role in regulating nociception and the healing process in tendinopathy.	Mentioned	The paratenon serves as a major site for nerve fibers, including SP- and CGRP-positive fibers, in both normal and tendinopathic conditions. During tendon healing, nerve ingrowth occurs in both the tendon proper and the paratenon, highlighting its role in early nerve regeneration and nociception regulation. The increased presence of nerve fibers in the paratenon during tendinopathy suggests its involvement in pain and inflammation associated with the condition.
Alfredson et al. (24)	2003	Mentioned	Vascular-neural ingrowth, involving new blood vessels and accompanying nerve fibers, identified by PGP9.5, is a significant source of pain in chronic Achilles tendinosis. This nerve ingrowth, detected near neovessels in affected tendons, likely plays a key role in the pain associated with tendinopathy.	Mentioned	The study describes the outcome of injecting a local anesthetic toward the neovessels outside the ventral part of the tendon, resulting in temporary pain relief during tendon-loading activities for all patients. This finding suggests that neovessels and accompanying neoinnervation in the peritendinous tissue could be a source of pain in tendinopathy.
Ackermann et al. (39)	2002	Mentioned	The findings during tendon healing demonstrate significant plasticity of the peripheral nervous system. The increase in GAP and PGP up to week 6 after the rupture and the following decline until week 16 likely reflects new nerve fiber ingrowth, which may serve as "transport channels" for specific mediators during connective tissue healing. Notably, during the regenerative phase (weeks one-6 after the rupture), there was a marked shift in neuronal immunoreactivity from the surrounding loose connective tissue to the proper tendinous tissue. The extensive ingrowth of GAP-immunoreactivity into the healing area suggests a crucial neuronal role in tendon regeneration.	Mentioned	During the regenerative phase (weeks one-6 after the rupture), there was a notable shift in neuronal immunoreactivity from the surrounding loose connective tissue to the proper tendinous tissue. While both the paratenon of ruptured and intact contralateral tendons consistently showed immunoreactivity to GAP-43 and PGP 9.5, only the ruptured tendon displayed this immunoreactivity in the proper tendinous tissue. This expression began at the first week after the rupture, peaked at week 6, and then gradually declined until week 16.
Alfredson et al. (19)	2001	Not mentioned	Not mentioned but found that glutamate may have a significant role in tendon pain in jumper's knee patients.	Mentioned	NMDAR1 immunoreactivity was observed in tracts of loose connective tissue, often alongside blood vessels. The study demonstrated the presence of NMDAR1 receptors associated with nerves in patellar tendons and linked chronic patellar tendon pain (jumper's knee) to high concentrations of the excitatory neurotransmitter glutamate.
Sanchis-Alfonso et al. (21)	2001	Mentioned	S-100 analysis revealed free myelinated fibers exhibiting a histologic pattern of "nerve sprouting" in the osteotendinous zone.	Not mentioned	Not mentioned