

RESEARCH

Open Access



Sequential vascular and neural changes underlying the progression of patellar tendinopathy

Jinsung Park^{1†}, Naoki Takemoto^{2†}, Tae-Hwan Kim^{1,3}, Junsuke Nakase^{2*} and Jin Kyu Lee^{1,4*}

Abstract

Purpose To investigate the temporal sequence of vascular, neural, and extracellular matrix (ECM) changes during the progression of collagenase-induced patellar tendinopathy and to test the hypothesis that early angiogenesis initiates a cascade leading to neural remodeling and tendon degeneration.

Methods A collagenase-induced rat patellar tendinopathy model was established in 40 male Sprague–Dawley rats. Animals were divided into one control group (PBS injection, n = 8, sacrificed at 12 weeks) and four experimental groups (collagenase type I injection, n = 8 each, sacrificed at 2, 4, 8, and 12 weeks post-injection). Histological evaluation (H&E and Masson's trichrome staining), immunohistochemistry, immunofluorescence (CD31, α -SMA, CGRP), and RT-qPCR for *Col1a1*, *Col3a1*, decorin (*Dcn*), and tenascin C (*Tnc*) were performed. Semi-quantitative scoring of cellularity, fibrosis, and vascularity was applied. Statistical analysis was conducted using ANOVA.

Results Histology revealed progressive hypercellularity, fibrosis, and calcification, with significant increases in cellularity from week 8 and in vascularity from week 4. Immunofluorescence showed CD31-positive cells increasing significantly at week 4, followed by α -SMA-positive and CGRP-positive cells at week 8. mRNA analysis demonstrated early peaks of *Col3a1*, *Dcn*, and *Tnc* expression at 2 weeks, while *Col1a1* expression peaked at 8 weeks and declined sharply by week 12. The *Col1a1/Col3a1* ratio was significantly elevated at 8 weeks before decreasing at 12 weeks.

Conclusion This study demonstrates a sequential progression in collagenase-induced patellar tendinopathy, where early angiogenesis precedes neural remodeling and ECM turnover. These findings suggest that vascular remodeling may be associated with subsequent neural and structural changes during tendinopathy progression.

Keywords Patellar tendinopathy, Angiogenesis, Neural remodeling (CGRP), Collagenase-induced tendinopathy model

[†]Jinsung Park and Naoki Takemoto have contributed equally to this work.

*Correspondence:
Junsuke Nakase
nakase1007@yahoo.co.jp
Jin Kyu Lee
jkleee77@hanyang.ac.kr

¹Hanyang University Institute for Rheumatology Research, Seoul, Republic of Korea

²Department of Orthopaedic Surgery, Graduate School of Medical Sciences, Kanazawa University, Kanazawa, Ishikawa, Japan

³Department of Rheumatology, Hanyang University Hospital for Rheumatic Disease, Seoul, Republic of Korea

⁴Department of Orthopaedic Surgery, Hanyang University Hospital, Seoul, Republic of Korea



© The Author(s) 2026. **Open Access** This article is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License, which permits any non-commercial use, sharing, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if you modified the licensed material. You do not have permission under this licence to share adapted material derived from this article or parts of it. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by-nc-nd/4.0/>.

Introduction

Patellar tendinopathy is a prevalent chronic overuse tendon disorder characterized by anterior knee pain, impaired function, and histopathological tendon degeneration [1]. The condition commonly affects athletes participating in repetitive jumping and loading activities, and remains a clinically challenging disorder because symptoms may persist for prolonged periods and significantly impair return to sport [2–6]. Histologically, tendinopathy is marked by collagen fiber disorganization, hypercellularity, fibrosis, neovascularization, and, in advanced stages, calcification and ossification [7–10]. Several mechanisms have been proposed to explain the pathogenesis of patellar tendinopathy, including repetitive mechanical overload, failed healing responses, vascular ingrowth, and neuronal mechanisms associated with pain generation; however, the temporal relationship among these biological events remains incompletely understood [4, 11].

Animal studies using collagenase-induced models have significantly contributed to the understanding of the pathophysiology of tendinopathy. These models reproduce key features observed in human disease, including ECM disruption, angiogenesis, and sensory nerve ingrowth [12, 13]. Importantly, recent findings suggest that vascular changes occur early in the disease process, potentially preceding neural remodeling, and may act as a trigger for subsequent degenerative and nociceptive changes [14, 15]. However, most existing studies have focused on isolated aspects, such as histopathology or molecular alterations at single time points, without fully integrating sequential vascular, neural, and molecular events across disease progression [8, 12, 16, 17]. Moreover, although ECM proteins such as type I and III collagens, Dcn, and Tnc are known to regulate tendon healing and remodeling, their temporal expression patterns in relation to vascular and neural changes remain poorly defined [18–21]. Despite extensive clinical investigation and various therapeutic efforts, the biological mechanisms governing the initiation and progression of patellar tendinopathy remain incompletely understood [6, 22–24]. Understanding these sequential events is essential because aberrant vascularization and sensory nerve ingrowth are closely linked to pain and impaired tendon healing in chronic tendinopathy.

Therefore, we utilized a collagenase-induced rat patellar tendinopathy model to examine time-dependent changes in histopathology, vascularization, sensory nerve remodeling, and expression of key extracellular matrix components, hypothesizing that early angiogenesis initiates a cascade leading to subsequent neural remodeling and progressive tendon degeneration.

Materials and methods

Animal

The rat study protocol (2024-0372A) was reviewed and approved by the Animal Experiments Ethics Committee of Hanyang University Institutional Animal Care and Use Committee. Sprague–Dawley (SD) rats were purchased from KOATECH (Pyeongtaek, Republic of Korea). Only specific pathogen-free animals were included, and any rats exhibiting abnormalities or signs of illness during the acclimation period preceding the experiment were excluded. Forty 10-week-old male rats were used in this study. Excluding the control group ($n=8$), the experimental animals received an injection of collagenase type I (Gibco; 0.015 g/ml) in the patellar tendon and were subsequently randomly allocated into four experimental groups based on time after treatment ($n=8$ rats per group). Animals were euthanised using a carbon dioxide (CO_2) chamber. CO_2 was gradually introduced into the chamber at a controlled flow rate to induce unconsciousness, followed by continued exposure to ensure death. Death was confirmed by the absence of respiration and heartbeat prior to tissue harvesting. This method was selected in accordance with institutional animal care and use committee (IACUC) guidelines and established humane endpoints for laboratory rodents.

Study design

In this study, a patellar tendinopathy model was induced in male SD rats (11 weeks old, average body weight 250 g) to evaluate time-dependent changes. Ten-week-old rats were purchased and acclimated for 1 week prior to experimentation. The animals were anesthetized using inhaled isoflurane at concentrations of 2–4% (4% for induction and 2% for maintenance). After shaving the knee area and positioning the limb at a 90° angle to expose the patellar tendon, 20 μl of 1.5% type I collagenase solution (0.015 g/ml in 1 $\times$ PBS) was injected into the patellar tendon using a 31-gauge needle. Animals were sacrificed at 2, 4, 8, and 12 weeks after collagenase injection, with $n=8$ per time point for RNA and histological analyses. The entire PBS-injected control group was sacrificed at 12 weeks for comparison (Fig. 1A, B). The work has been reported in line with the ARRIVE guidelines 2.0

Histology

For histological evaluation, hematoxylin and eosin (H&E) staining and Masson's trichrome (MT) staining were performed following standard procedures. For H&E staining, tissue sections were deparaffinized, rehydrated, stained with hematoxylin for 3 min, rinsed in running tap water, counterstained with eosin for 1 min, dehydrated, and mounted. For MT staining, sections were treated according to the manufacturer's instructions to visualize total collagen content. All stained slides were mounted

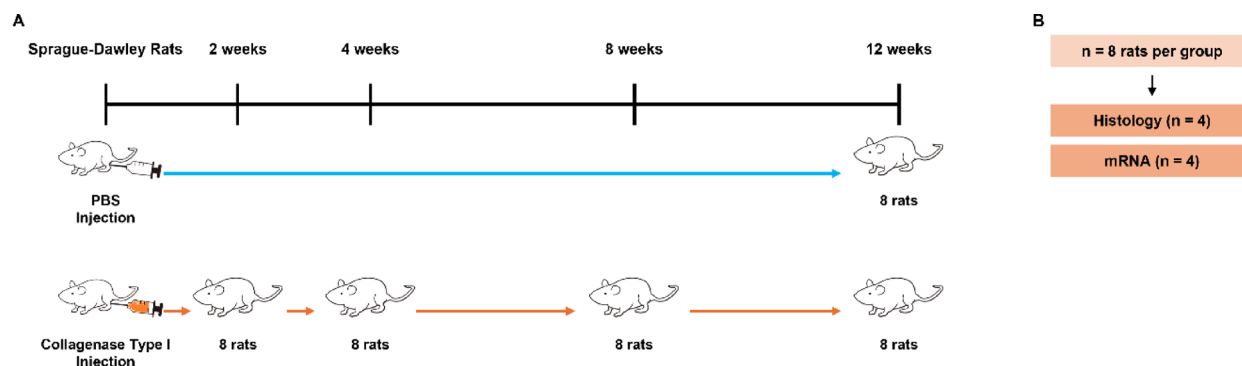


Fig. 1 **A** Schematic of the animal experimental protocol. **B** Distribution of animals per group used for histology and mRNA analysis

using a permanent mounting medium. Four samples per group were analyzed. Histological images were captured at $\times 40$ and $\times 100$ magnifications, focusing on both the PT middle 1/3 and PT proximal 1/3 regions. Histological evaluation of the rat infrapatellar fat pad was performed using a previously established semi-quantitative scoring system based on three parameters: cellularity, fibrosis, and vascularity. Each parameter was graded on a scale from 0 to 3. Cellularity was assessed based on the distribution and density of cells. A score of 0 indicated scattered cells, 1 indicated focal clustering, 2 indicated a diffuse increase in cellularity, and 3 represented a severe diffuse increase. Fibrosis was evaluated as the percentage of fibrotic tissue within the image area. A score of 0 indicated absence of fibrosis ($< 10\%$ of the image area), 1 indicated mild fibrosis ($10\text{--}30\%$), 2 indicated moderate fibrosis ($30\text{--}60\%$), and 3 indicated severe fibrosis ($> 60\%$). Vascularity was scored according to the number of blood vessels observed in each field. A score of 0 represented no vessels present, 1 indicated 1–2 vessels, 2 indicated 3–4 vessels, and 3 indicated five or more vessels. Scoring was performed on H&E-stained sections at $\times 40$ magnification.

Immunohistochemistry

Immunohistochemical staining was conducted according to standard procedures. Briefly, tissue slides were deparaffinized using Neoclear and rehydrated through a graded series of ethanol solutions (100% to 70%), followed by rinsing in distilled water. Following three washes with $1\times$ PBS, slides were permeabilized with 0.3% Triton X-100 in PBS for 10 min. Antigen retrieval was then performed by incubating the slides with Proteinase K at 37°C for 10 min, followed by an additional 10 min at room temperature. Slides were subsequently washed three times with $1\times$ PBS, and nonspecific binding was blocked using a commercial blocking reagent for 30 min at room temperature. Slides were then incubated with primary antibodies (CGRP and collagen I), diluted in antibody diluent for 1 h at room temperature

and then in a secondary antibody for 30 min, followed by staining and visualization using an ABC kit and DAB substrate kit. Slides were counterstained with hematoxylin for 10 s, dehydrated through a graded ethanol series (50–100%), and mounted with a permanent mounting medium. Images were acquired using a Nikon Eclipse Ti-U microscope at $\times 200$ magnification. For each group, four samples were analyzed. CGRP-positive cells were semi-quantitatively evaluated by counting the number of positively-stained cells in images.

Immunofluorescence

Immunofluorescence staining was performed according to standard protocols. Briefly, paraffin-embedded tissue slides were deparaffinized using Neoclear and rehydrated through a graded ethanol series (100 to 70%), followed by rinsing in distilled water. After three washes with $1\times$ PBS, slides were permeabilized with 0.3% Triton X-100 in PBS for 10 min. Antigen retrieval was performed by incubating the slides with Proteinase K at 37°C for 10 min, followed by an additional 10 min at room temperature. Slides were subsequently washed three times with $1\times$ PBS. Non-specific binding was blocked using a commercial blocking reagent for 30 min at room temperature. Slides were incubated overnight at 4°C with primary antibodies against CD31 (green), α -SMA (red), and CGRP (yellow), all diluted in antibody diluent. Following primary antibody incubation, slides were washed three times with $1\times$ PBST. The sections were then incubated for 1 h at room temperature with fluorophore-conjugated secondary antibodies: Alexa Fluor 488-conjugated donkey anti-goat IgG for CD31, Alexa Fluor 555-conjugated donkey anti-mouse IgG for α -SMA, and Alexa Fluor 647-conjugated donkey anti-rabbit IgG for CGRP. DAPI (blue) was included in the secondary antibody solution for nuclear counterstaining. After secondary antibody incubation, slides were again washed three times with $1\times$ PBST. Finally, the stained slides were mounted using a fluorescence-compatible mounting medium and coverslipped to preserve signal and prevent photobleaching.

Fluorescent images were acquired at $\times 1000$ magnification using a Stellaris 5 LIA confocal microscope.

RT-qPCR

For mRNA analysis, rat patellar tendon tissues were carefully dissected and finely chopped using sterile scissors. The chopped tissue was then processed using a tissue homogenizer. The resulting homogenates were incubated with TRIzol reagent for 1 h at room temperature on a tube rotator to ensure thorough mixing and complete cell lysis. Total RNA was subsequently isolated using a TRIzol-based extraction method, following standard protocols. A total of 500 ng of RNA was used for complementary DNA (cDNA) synthesis using reverse transcriptase. The synthesized cDNA was then used as the template for real-time quantitative PCR (RT-qPCR). The following primer sequences were used: *Col1a1* forward, 5'-TGACTGGAAGAGCGGAGAGTA-3'; *Col1a1* reverse, 5'-CATGCTTCTTCTCCTTGGGGT-3'; *Col3a1* forward, 5'-AAT AATGGCAGTCCTGGTGGG-3'; *Col3a1* reverse, 5'-GCTCTCCCTTTGCTCCATTCT-3'; *Dcn* forward, 5'-CCTTACGACCCGTACAATCCC-3'; *Dcn* reverse, 5'-CCAGGGTACTTTGTCCAGACC-3'; *Tnc* forward, 5'-TGAACGAAGTGGCCACATCTC-3'; *Tnc* reverse, 5'-CTTCCGGTTCAGCTTCTGTGG-3'; *Gapdh* forward, 5'-TGGGTGTGAACCACGAGAAAT-3'; *Gapdh* reverse, 5'-CACAGTCTTCTGAGTGGCAGT-3'. The ratio of collagen I to collagen III, which is commonly used as a marker for connective tissue maturation, was calculated based on their mRNA expression levels using fold change values.

Statistical analysis

Quantitative and statistical analyses of the graph data were performed using GraphPad Prism 7.0 software. Differences between the control group and each experimental group at the indicated time points were assessed using a one-way analysis of variance (ANOVA) followed by Dunnett's post hoc test for multiple comparisons. Data are expressed as the mean $\pm$ standard error of the mean (SEM) from at least four independent experiments. Asterisks indicate statistical significance (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$).

Results

Histological features in a rat patellar tendinopathy model

As patellar tendinopathy progressed following collagenase I injection, H&E and MT staining were performed to evaluate the infrapatellar fat pad histologically. With pathological progression, the cell morphology became rounded, hypercellularity was observed, and calcification developed in the tendon by week 12 (Fig. 2A, B). Compared with the control group, cellularity increased significantly from 8 weeks ($p < 0.01$), fibrosis at 12 weeks

($p < 0.05$), vascularity at 4 weeks ($p < 0.05$), and the total grade from 8 weeks ($p < 0.01$) (Fig. 2C).

Analysis of angiogenic and neural proteins

Given that histological analyses demonstrated an early increase in vascularity beginning at week 4 during disease progression (Fig. 2), we next examined sensory nerve remodeling using CGRP, a well-established marker for nociceptive nerve activity. As the disease progressed, CGRP expression increased (Fig. 3A), with a significant ($p < 0.01$) increase in the number of CGRP-positive cells observed beginning at week 8 (Fig. 3B). Immunofluorescence staining revealed that, as tendinopathy progressed, CD31 (vascular endothelium), α -SMA (vascular smooth muscle cell marker), and CGRP (sensory nerve fiber marker) expression increased in both the proximal and middle thirds of the patellar tendon (Fig. 4A, B). Specifically, compared with the control group, the number of CD31-positive cells increased significantly from week 4 ($p < 0.05$), whereas α -SMA-positive cells ($p < 0.01$) and CGRP-positive cells ($p < 0.001$) showed significant increases from week 8 (Fig. 4C).

Gene expression of collagen and tendon regeneration markers

mRNA expression analysis revealed a significant ($p < 0.001$) increase in type I collagen gene expression at 8 weeks, reaching its peak level at this time point. Notably, the expression level sharply declined by 12 weeks. In contrast, type III collagen gene expression was significantly ($p < 0.05$) elevated at the early time point of 2 weeks, peaked at this stage, and gradually decreased until 12 weeks. Similarly, *Dcn* ($p < 0.001$) and *Tnc* ($p < 0.01$), both known to be involved in the early phase of tendon regeneration, exhibited significantly increased expression at 2 weeks, which subsequently declined over the course of the study period (Fig. 5A). Moreover, the ratio of type I collagen to type III collagen gene expression was significantly ($p < 0.001$) increased at 8 weeks and markedly decreased by 12 weeks (Fig. 5B).

Discussion

In the present study, we identified a distinct temporal sequence in the progression of collagenase-induced patellar tendinopathy. Angiogenesis was observed as early as 4 weeks, preceding the onset of sensory nerve remodeling at 8 weeks. In parallel, the expression of the ECM markers type III collagen, *Dcn*, and *Tnc* significantly increased at 2 weeks before gradually declining, whereas type I collagen expression peaked at 8 weeks and then sharply decreased by 12 weeks. These results suggest that vascular remodeling serves as an early initiating event, followed by neural infiltration and matrix

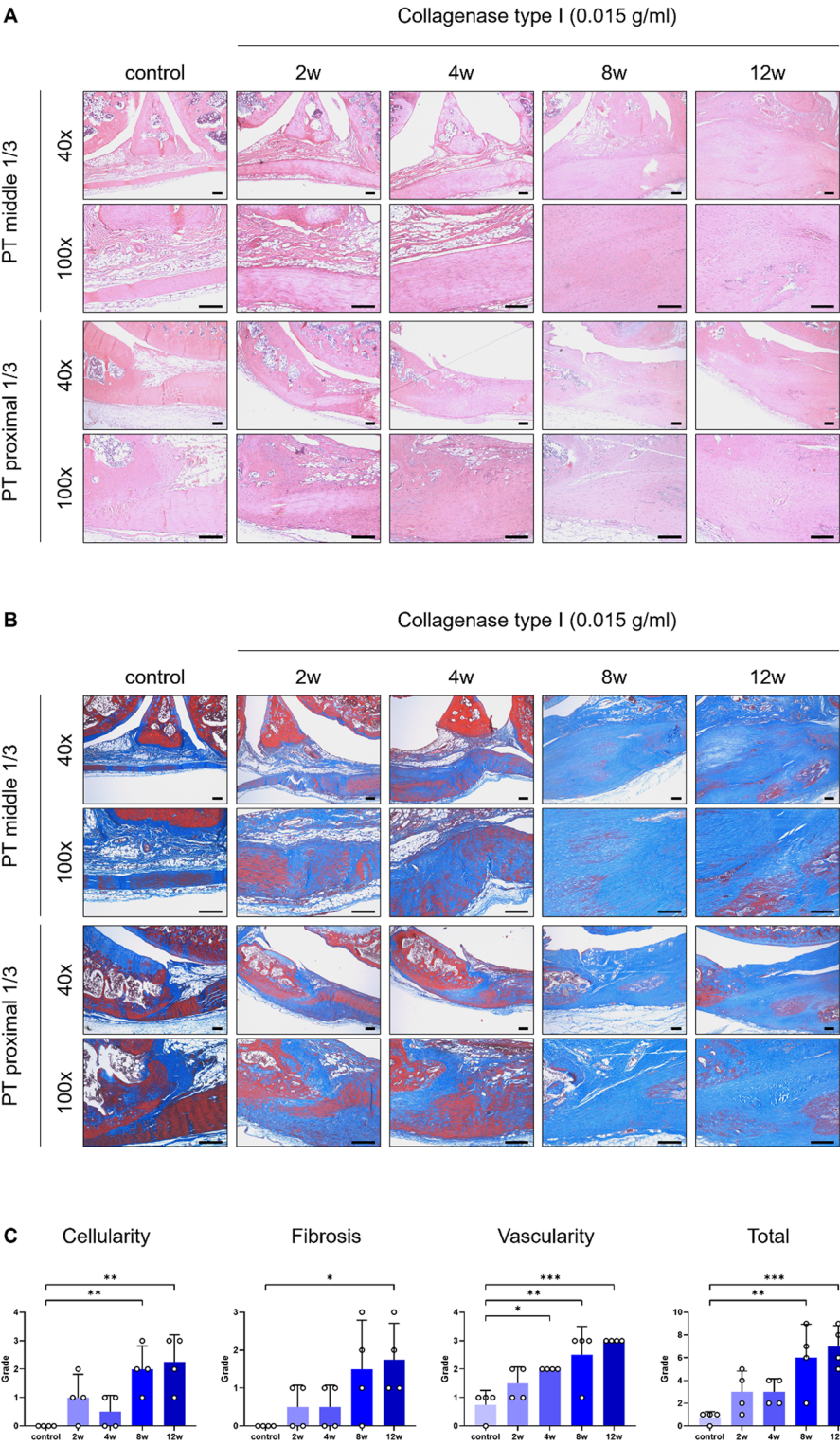


Fig. 2 **A** Representative H&E staining of patellar tendon at 2, 4, 8, and 12 weeks post-treatment compared with control. magnification×40 and×100, scale bar: 200 μm. **B** Representative Masson's trichrome staining of patellar tendon at 2, 4, 8, and 12 weeks post-treatment compared with control. magnification×40 and×100, scale bar: 200 μm. **C** Histological grading of the infrapatellar fat pad. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; ns: not significant. Statistical analysis of the data was performed using a one-way analysis of variance. Data are shown as mean ± standard error of the mean (n=4 per group)

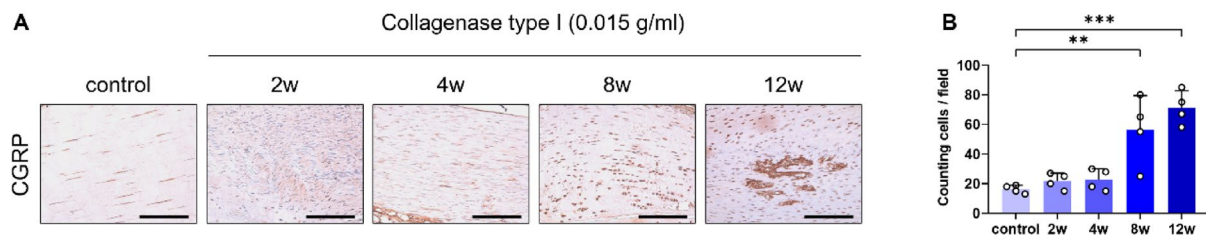


Fig. 3 **A** Representative IHC staining showing CGRP protein expression in patellar tendon tissues. magnification $\times 200$, scale bar: 200 μm . **B** Semi-quantitative analysis of CGRP-positive cells per field in the corresponding tendon sections. $*p < 0.05$; $**p < 0.01$; $***p < 0.001$; ns: not significant. Statistical analysis of the data was performed using a one-way analysis of variance. Data are shown as mean $\pm$ standard error of the mean (n = 4 per group)

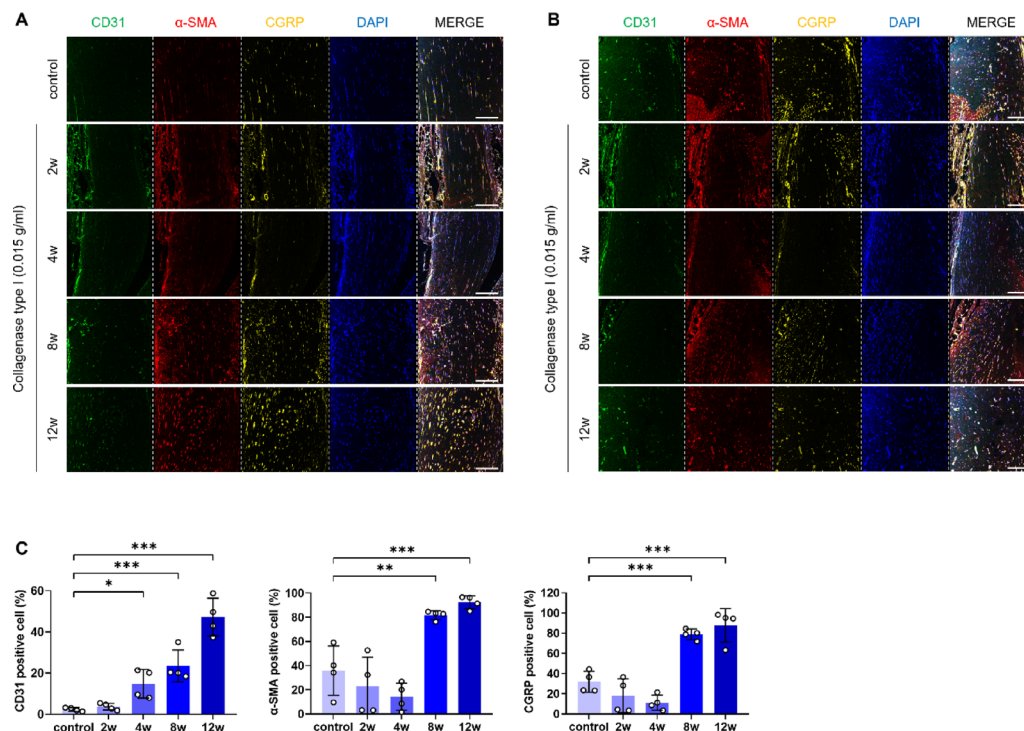


Fig. 4 **A** Representative immunofluorescence images of the patellar tendon middle 1/3, showing CD31 (green), α-SMA (red), CGRP (yellow), and nuclei stained with DAPI (blue), along with merged images. Magnification $\times 1000$, scale bar: 40 μm . **B** Representative immunofluorescence images of the patellar tendon proximal 1/3, showing CD31 (green), α-SMA (red), CGRP (yellow), and nuclei stained with DAPI (blue), along with merged images. Magnification $\times 1000$, scale bar: 40 μm . **C** Semi-quantitative analysis showing the percentage of CD31-, α-SMA-, and CGRP-positive cells. $*p < 0.05$; $**p < 0.01$; $***p < 0.001$; ns: not significant. Statistical analysis of the data was performed using a one-way analysis of variance. Data are shown as mean $\pm$ standard error of the mean (n = 4 per group)

turnover, leading to structural degeneration and failed tendon healing.

Our findings align with previous clinical and experimental studies reporting that neovascularization frequently accompanies symptomatic tendinopathy and often correlates with regions of pain and tissue disorganization [25–27]. Doppler ultrasound and histological investigations have consistently shown increased vascularity in degenerative tendons, with the extent of angiogenesis paralleling symptom severity [7, 28]. The observation of vascular changes at 4 weeks in our model

supports angiogenesis as one of the earliest responses to tendon injury. Moreover, the subsequent appearance of sensory nerve remodeling at 8 weeks echoes reports that nociceptive innervation often follows vascular proliferation, potentially through shared molecular mediators such as vascular endothelial growth factor (VEGF), nerve growth factor (NGF), and substance P, which can promote both endothelial and neuronal growth [29, 30]. This temporal relationship suggests that early vascular changes may create a permissive microenvironment for later neural invasion, linking angiogenesis not only to

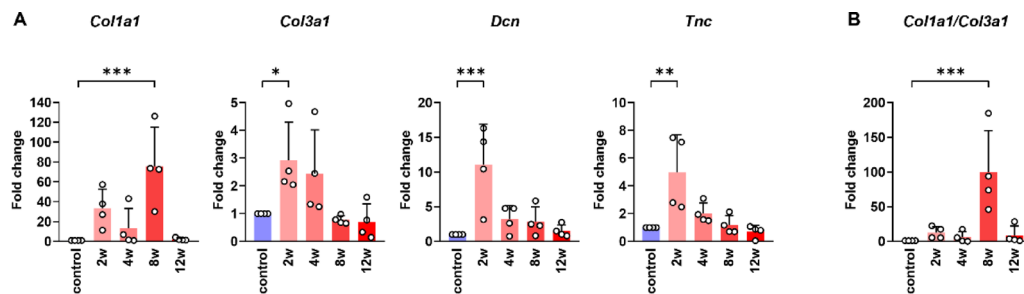


Fig. 5 **A** Quantitative PCR analysis of mRNA expression levels of *Col1a1*, *Col3a1*, *Dcn*, and *Tnc* in patellar tendon tissues. **B** Ratio of *Col1a1/Col3a1* mRNA expression. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; ns: not significant. Statistical analysis of the data was performed using a one-way analysis of variance. Data are shown as mean $\pm$ standard error of the mean ($n = 4$ per group)

structural degeneration but also to pain development in tendinopathy. Mechanistically, the observed temporal sequence of angiogenesis followed by neural remodeling may be explained by shared regulatory pathways involved in vascular-neural interactions. VEGF, a key mediator of angiogenesis, has also been implicated in promoting sensory nerve ingrowth, while NGF contributes to both nociceptive signaling and neurovascular coupling. These factors may contribute to a microenvironment that facilitates the coordinated progression of vascular and neural changes observed in tendinopathy. Importantly, similar pathological features have been reported in human patellar tendinopathy, including increased neovascularization, sensory nerve ingrowth, and altered extracellular matrix composition. Clinical imaging studies, such as Doppler ultrasound, have demonstrated a correlation between neovascularization and pain, supporting the relevance of vascular-neural interactions in symptomatic tendinopathy. While these similarities support the relevance of our findings, important differences should be considered. In particular, human tendinopathy is typically a chronic, multifactorial condition influenced by long-term mechanical loading and systemic factors, whereas the present model represents an acute, enzyme-induced injury. These differences may affect the progression and underlying mechanisms of the disease and should be taken into account when interpreting the translational significance of our results. The early and transient upregulation of type III collagen observed in our study is consistent with the well-established paradigm of tendon healing in which type III collagen predominates during the initial proliferative phase before being replaced by type I collagen to restore tensile strength [31, 32]. However, persistent type III collagen expression or an elevated type III to type I collagen ratio has been associated with mechanically inferior scar tissue and chronic tendon dysfunction [33, 34]. The early peaks of *Dcn* and *Tnc* expression similarly reflect their roles in collagen fibrillogenesis, cell-matrix interactions, and modulation of growth factor signaling during the early stages of repair [21, 35, 36]. These findings collectively indicate that tendon healing

initially attempts to recapitulate developmental programs characterized by ECM deposition and vascular invasion, but that dysregulation of this sequence may underlie the transition from acute injury to chronic degeneration.

Taken together, these findings indicate a temporal association among angiogenesis, neural remodeling, and ECM turnover in tendinopathy progression. While this temporal pattern provides insight into disease mechanisms, several limitations should be acknowledged. This study was conducted using only male Sprague-Dawley rats, which may limit the generalizability of the findings, as sex-related differences may influence disease progression. In addition, differences between rodent and human tendon biology may restrict direct clinical translation. Furthermore, this study focused on histological and molecular analyses without functional assessments such as biomechanical testing or pain-related behavioral evaluation. The present study was designed to primarily elucidate the temporal sequence of pathological changes rather than to assess functional outcomes. Although a temporal sequence was identified, causality between angiogenesis and subsequent changes was not established. This limitation is particularly important, as the current findings are based on temporal associations rather than direct mechanistic evidence. Therefore, it cannot be concluded that angiogenesis directly drives neural remodeling or ECM degeneration. In addition, the small sample size and the use of semi-quantitative analytical methods may limit the robustness of the findings. Future studies incorporating functional outcomes and interventional approaches will be necessary to further validate these findings and clarify underlying mechanisms.

Conclusions

In summary, our study demonstrates that early angiogenesis precedes neural remodeling and extracellular matrix changes during the progression of collagenase-induced patellar tendinopathy, suggesting that vascular remodeling may contribute to subsequent neural and structural alterations leading to tendon degeneration.

Author contributions

J. Park: Writing—original draft, Formal analysis, Investigation, Methodology, Data curation, Visualization, N. Takemoto: Writing—original draft, Conceptualization, Investigation, T-H. Kim: Validation, Funding acquisition, J. Nakase: Writing—review & editing, Conceptualization, Supervision, J. K. Lee: Writing—review & editing, Validation, Resources, Funding acquisition, Project administration, Supervision.

Funding

This research was funded by the National Research Foundation of Korea (grant number: 2021R1A6A1A03038899) and the Korean Fund for Regenerative Medicine (KFRM) grant funded by the Korea government (the Ministry of Science and ICT, the Ministry of Health & Welfare) (grant number: RS-2023-00215515).

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participant

The rat study protocol (approval number 2024-0372A) was reviewed and approved by the Animal Experiments Ethics Committee of Hanyang University Institutional Animal Care and Use Committee.

Competing interests

The authors declare that they have no competing interests.

Received: 24 February 2026 / Accepted: 21 May 2026

Published online: 15 June 2026

References

1. Theodorou A, Komnos G, Hantes M. Patellar tendinopathy: an overview of prevalence, risk factors, screening, diagnosis, treatment and prevention. *Arch Orthop Trauma Surg.* 2023;143(11):6695–705.
2. Nutarelli S, da Lodi CMT, Cook JL, Deabate L, Filardo G. Epidemiology of patellar tendinopathy in athletes and the general population: a systematic review and meta-analysis. *Orthop J Sports Med.* 2023;11(6):23259671231173659.
3. Aicale R, Oliviero A, Maffulli N. Management of Achilles and patellar tendinopathy: what we know, what we can do. *J Foot Ankle Res.* 2020;13(1):59.
4. Aicale R, Bisaccia RD, Oliviero A, Oliva F, Maffulli N. Current pharmacological approaches to the treatment of tendinopathy. *Expert Opin Pharmacother.* 2020;21(12):1467–77.
5. Aicale R, Tarantino D, Maffulli N. Surgery in tendinopathies. *Sports Med Arthrosc Rev.* 2018;26(4):200–2.
6. Furia JP, Rompe JD, Cacchio A, Del Buono A, Maffulli N. A single application of low-energy radial extracorporeal shock wave therapy is effective for the management of chronic patellar tendinopathy. *Knee Surg Sports Traumatol Arthrosc.* 2013;21(2):346–50.
7. Fu SC, Rolf C, Cheuk YC, Lui PP, Chan KM. Deciphering the pathogenesis of tendinopathy: a three-stages process. *Sports Med Arthrosc Rehabil Ther Technol.* 2010;2:30.
8. Vidal L, Lopez-Garzon M, Venegas V, et al. A novel tendon injury model, induced by collagenase administration combined with a thermo-responsive hydrogel in rats, reproduces the pathogenesis of human degenerative tendinopathy. *Int J Mol Sci.* 2024. <https://doi.org/10.3390/ijms25031868>.
9. Oliva F, Via AG, Maffulli N. Physiopathology of intratendinous calcific deposition. *BMC Med.* 2012;10:95.
10. Abate M, Silbernagel KG, Siljeholm C, et al. Pathogenesis of tendinopathies: inflammation or degeneration? *Arthritis Res Ther.* 2009;11(3):235.
11. Morton S, Chan O, King J, et al. High volume image-guided injections for patellar tendinopathy: a combined retrospective and prospective case series. *Muscles Ligaments Tendons J.* 2014;4(2):214–9.
12. Perucca Orfei C, Lovati AB, Vigano M, et al. Dose-related and time-dependent development of collagenase-induced tendinopathy in rats. *PLoS ONE.* 2016;11(8):e0161590.
13. Luo J, Wang Z, Tang C, et al. Animal model for tendinopathy. *J Orthop Translat.* 2023;42:43–56.
14. Scott A, Backman LJ, Speed C. Tendinopathy: update on pathophysiology. *J Orthop Sports Phys Ther.* 2015;45(11):833–41.
15. Gehwolf R, Tempfer H, Cesur NP, Wagner A, Traweger A, Lehner C. Tendinopathy: the interplay between mechanical stress, inflammation, and vascularity. *Adv Sci.* 2025;12(36):e06440.
16. Kitagawa T, Nakase J, Takata Y, Shimozaki K, Asai K, Tsuchiya H. Histopathological study of the infrapatellar fat pad in the rat model of patellar tendinopathy: a basic study. *Knee.* 2019;26(1):14–9.
17. Lui PP, Liang Z, Tan RM, Yung PSH. Establishment of a mouse degenerative model of patellar tendinopathy with upregulation of inflammation. *Int J Mol Sci.* 2024. <https://doi.org/10.3390/ijms25073847>.
18. Leahy TP, Fung AK, Weiss SN, Dyment NA, Soslosky LJ. Investigating the temporal roles of decorin and biglycan in tendon healing. *J Orthop Res.* 2023;41(10):2238–49.
19. Yang G, Rothrauff BB, Tuan RS. Tendon and ligament regeneration and repair: clinical relevance and developmental paradigm. *Birth Defects Res C Embryo Today.* 2013;99(3):203–22.
20. Sharma P, Maffulli N. Biology of tendon injury: healing, modeling and remodeling. *J Musculoskelet Neuronal Interact.* 2006;6(2):181–90.
21. Tashjian RZ, Zitnay J, Kazmers NH, et al. Tenascin C deletion impairs tendon healing and functional recovery after rotator cuff repair. *J Orthop Res.* 2025;43(3):483–91.
22. Maffulli N, Oliva F, Loppini M, Aicale R, Spiezia F, King JB. The Royal London Hospital test for the clinical diagnosis of patellar tendinopathy. *Muscles Ligaments Tendons J.* 2017;7(2):315–22.
23. Maffulli N, Giai Via A, Oliva F. Revision surgery for failed patellar tendinopathy exploration. *Sports Med Arthrosc Rev.* 2017;25(1):36–40.
24. Maffulli N, Del Buono A, Oliva F, Testa V, Capasso G, Maffulli G. High-volume image-guided injection for recalcitrant patellar tendinopathy in athletes. *Clin J Sport Med.* 2016;26(1):12–6.
25. Cook JL, Malliaras P, De Luca J, Ptasznik R, Morris ME, Goldie P. Neovascularization and pain in abnormal patellar tendons of active jumping athletes. *Clin J Sport Med.* 2004;14(5):296–9.
26. Hoksud A, Ohberg L, Alfredson H, Bahr R. Ultrasound-guided sclerosis of neovessels in painful chronic patellar tendinopathy: a randomized controlled trial. *Am J Sports Med.* 2006;34(11):1738–46.
27. Mersmann F, Domroes T, Tsai MS, et al. Longitudinal evidence for high-level patellar tendon strain as a risk factor for tendinopathy in adolescent athletes. *Sports Med.* 2023;9(1):83.
28. van Snellenberg W, Wiley JP, Brunet G. Achilles tendon pain intensity and level of neovascularization in athletes as determined by color Doppler ultrasound. *Scand J Med Sci Sports.* 2007;17(5):530–4.
29. Ackermann PW, Phisitkul P, Pearce CJ. Achilles tendinopathy—pathophysiology: state of the art. *J ISAKOS.* 2018;3(5):304–14.
30. Vasta S, Di Martino A, Zampogna B, Torre G, Papalia R, Denaro V. Role of VEGF, nitric oxide, and sympathetic neurotransmitters in the pathogenesis of tendinopathy: a review of the current evidences. *Front Aging Neurosci.* 2016;8:186.
31. Leong NL, Kator JL, Clemens TL, James A, Enamoto-Iwamoto M, Jiang J. Tendon and ligament healing and current approaches to tendon and ligament regeneration. *J Orthop Res.* 2020;38(1):7–12.
32. Singh D, Rai V, Agrawal DK. Regulation of collagen I and collagen III in tissue injury and regeneration. *Cardiol Cardiovasc Med.* 2023;7(1):5–16.
33. Lui PP, Chan LS, Lee YW, Fu SC, Chan KM. Sustained expression of proteoglycans and collagen type III/type I ratio in a calcified tendinopathy model. *Rheumatology (Oxford).* 2010;49(2):231–9.
34. Docheva D, Muller SA, Majewski M, Evans CH. Biologics for tendon repair. *Adv Drug Deliv Rev.* 2015;84:222–39.
35. Thorpe CT, Birch HL, Clegg PD, Screen HR. The role of the non-collagenous matrix in tendon function. *Int J Exp Pathol.* 2013;94(4):248–59.
36. Wagenhauser MU, Pietschmann MF, Sievers B, et al. Collagen type I and decorin expression in tenocytes depend on the cell isolation method. *BMC Musculoskelet Disord.* 2012;13:140.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.