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Basic Science

Journal of Orthopaedic Surgery

Journal of Orthopaedic Surgery
32(2) 1–8
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DOI: 10.1177/10225536241265827
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Biomechanical and histological evaluation of aspirin in rotator cuff tear rat model

Seok Won Chung[1], Seung Ho Chung[2], Dong-Hyun Kim[2], Hyun Joo Lee[2], Eugene J Park[2], Bum-Jin Shim[2], Chul-Hyun Cho[3] and Jong Pil Yoon[2]

Abstract

Background: Aspirin is a representative non-steroidal anti-inflammatory drug (NSAIDs) and has been commonly used for the treatment of tendinopathy in clinical practice. In this study, we aimed to evaluate the biomechanical and histological healing effects of aspirin on the healing of the tendon-to-bone interface after rotator cuff tear repair. **Methods:** A total of 20 male Sprague-Dawley rats were randomly divided into two groups of 10 rats each. Group-C performed repaironly, and group-aspirin treated with aspirin after tendon repair. Group-aspirin rat were intraperitoneally injected with aspirin at 10 mg/kg every 24 h for 7 days. Eight weeks after surgery, the left shoulder of each rat was used for histological analysis and the right shoulder for biomechanical analysis. **Results:** In the biomechanical analysis, there was no significant difference in load-to-failure (group-C: 0.61 ± 0.32 N, group-aspirin: 0.74 ± 0.91 N; p = .697) and ultimate stress (group-C: 0.05 ± 0.01 MPa, group-aspirin: 0.29 ± 0.43 MPa; p = .095). For the elongation (group-C: 222.62 ± 57.98%, group-aspirin: 194.75 ± 75.16%; p = .028), group-aspirin confirmed a lower elongation level than group-C. In the histological evaluation, the Bonar score confirmed significant differences in collagen fiber density (group-C: 1.60 ± 0.52, group-aspirin: 2.60 ± 0.52, p = .001) and vascularity (group-C: 1.00 ± 0.47, group-aspirin: 2.20 ± 0.63, p = .001) between the groups. **Conclusions:** Aspirin injection after rotator cuff tear repair may enhance the healing effect during the early remodeling phase of tendon healing.

Level of Evidence

A Comparative Animal Study

Keywords

NSAIDs, aspirin, biomechanical, histological, rotator cuff

Date received: 1 September 2023; Received revised 7 June 2024; accepted: 18 June 2024

[1]Department of Orthopaedic Surgery, School of Medicine, Konkuk University Medical Center, Seoul, Republic of Korea
[2]Department of Orthopaedic Surgery, School of Medicine, Kyungpook National University, Daegu, Republic of Korea
[3]Department of Orthopedic Surgery, Dongsan Hospital, Keimyung University School of Medicine, Daegu, Republic of Korea

Corresponding author:
Jong Pil Yoon, Department of Orthopaedic Surgery, School of Medicine, Kyungpook National University, Kyungpook National University Hospital, 130, Dongdeok-ro, Jung-gu, Daegu 41944, Republic of Korea.
Email: altjp1@gmail.com

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Introduction

Rotator cuff tears (RCT) are caused by extrinsic factors such as age, trauma, and strain, and endogenous factors such as tendon degeneration, poor blood supply, and subacromial impingement.[1–5] This results in a patient's pain such as shoulder pain, reduced muscle strength, and limited range of motion, resulting in an extremely reduced quality of life for the individual patient.[3] In general, RCT are classified according to the size of the tear: small (<1 cm), medium (1 to 3 cm), large (3 to 5 cm), and giant (>5 cm).[6] Massive RCT account for 40% of all rotator cuff tears and have a higher rate of recurrent tears after surgical repair due to structural failure and poor outcomes compared to small tears.[7] Effective surgical treatments are being used for this RCT healing, but the failure rate is still very high.[8,9] Above all, there is a lack of review of drugs that promote tendon healing in the early remodeling stage after rotator cuff tendon repair.[10,11]

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed to treat musculoskeletal pain and inflammation. NSAIDs act by inhibiting prostaglandin production by inhibiting cyclooxygenase (COX), an enzyme that converts arachidonic acid into prostaglandins, prostacyclin, and thromboxane.[12,13] The inhibition of these products causes a reduction of inflammation and also results in antipyretic, antithrombotic, and analgesic effects.[13,14] Aspirin, a representative (NSAIDs), has not only pain relief and anti-inflammatory effects in joint diseases but also enhanced cardiomyocyte differentiation of myeloid MSCs, tendinopathy, or tendon damage.[14–17] Clinical studies have shown that celecoxib, an NSAID, may negatively impact bone-tendon healing.[18] Additionally, research using rabbit models indicates that NSAIDs could delay tendon healing in the initial stages after tendon reconstruction.[19] These findings are crucial for selecting NSAIDs for pain management following tendon repair, highlighting the need for careful consideration of the potential effects on healing processes.

In the previous study showed that GDF7 induced by aspirin, a representative NSAID drug, played an important role in tenogenic healing and increased mechanical properties of micro damaged tendon.[15] In the same group, they reported that aspirin increased the biomechanical properties of damaged achilles tendons by inhibiting adipogenesis and fatty infiltration of tendon-derived stem cells (TDSCs) mediated by the regulation of PTEN/PI3K/AKT signaling pathway.[14] However, to the best of our knowledge, no study has yet examined the biomechanical and histological effects of aspirin on the healing process of the rotator cuff tendon-to-bone interface. In this paper, we evaluated the biomechanical and histological tendon healing effects of aspirin in early remodeling phage after rotator cuff repair.

Materials and methods

Animal model

All animal procedures were approved by the institutional animal commission at the author's institution. We used 9-week-old male Sprague–Dawley rats that were housed in a specific pathogen-free facility. Prior to the experimental process, the rats were acclimated to a 12 h/12 h light/dark cycle at 22°C ± 2°C for 1 week, and they were allowed unlimited access to food and water. The rat's right shoulder was used for the subsequent biomechanical evaluation, including assessment of ultimate failure load at 8 weeks, whereas the left shoulder was used for histological analysis. A total of 10 rats were randomly allocated into two groups (10 each): group-C, repair only, and group-aspirin, repair and aspirin treatment.

Surgical procedure

All animals were anesthetized using zolazepam (0.05–0.3 mL/kg, Zoletil®, Virbac S.A., Carros Cedex, France) and xylazine hydrochloride (0.15 mL/kg, Rompun®, Bayer HealthCare, Leverkusen, Germany).[20] This provided pain relief and muscle relaxation that helped these animals stay asleep. The rat's shoulders were shaved, sterilized, and subjected to a rotator cuff incision. Briefly, palpate the scapula and make a 3 cm longitudinal skin incision. The exposed deltoid muscle was incised and the supraspinatus tendon was identified. The supraspinatus tendon was cut with a blade at the tendon-to-bone area with metzembaum. The greater tubercle was widely exposed and two parallel bone tunnels were created using a needle. The supraspinatus tendon was repaired with the single-row technique through the tunnel using Ethibond (Ethicon, Somerville, NJ, USA). (Figure 1) The rats in the control group had no other interventions after rotator cuff incision. In the experimental group, aspirin (Bayer AG, Leverkusen, Germany) was intraperitoneally injected at a dose of 10 mg/kg/day for 1 week. No rats died after surgery until sacrifice, and no complications were observed before sacrifice. Four weeks after surgery, rats were euthanized to collect samples from both shoulders. To minimize pain, the rats were anesthetized with isoflurane and placed in a CO_2 chamber until no general movement was observed and death was confirmed.

Biomechanical analysis

For biomechanical measurements, the reattached tendon of the rat's right shoulder was appropriately excised

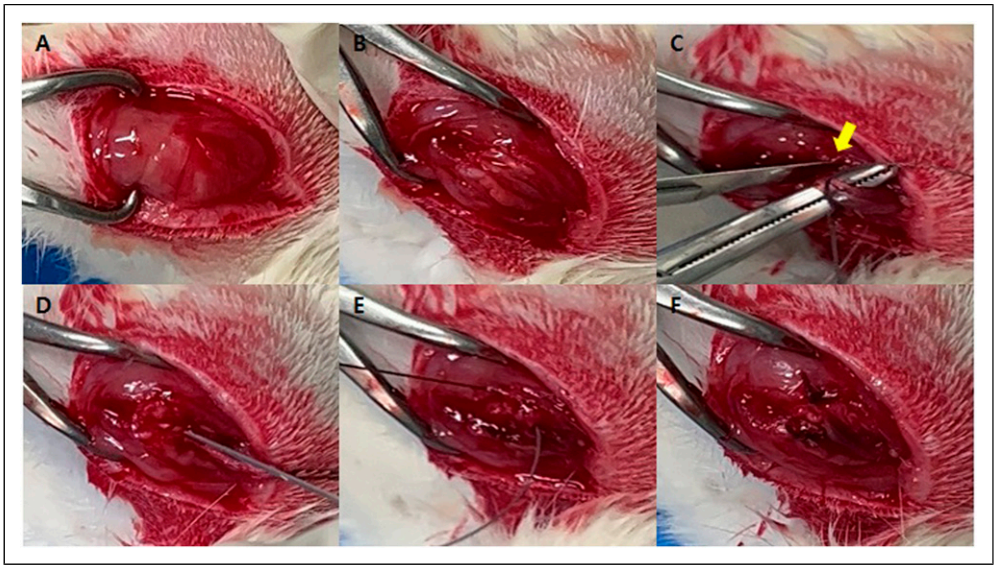

Figure 1. Surgical procedure for rotator cuff tear rat model. (A, B) The deltoid muscle was isolated to expose the SS tendon and (C) the tendon was cut in the tendon-to-bone interface (yellow arrow). The tendon cut SS muscle was labeled using Ethibond (Ethicon, Somerville, NJ, USA) thread, and (D) two holes were made with a needle in the deltoid for tendon reattachment. (E, F) The severed tendon was sutured to the deltoid.

(Figure 2(a)). A detailed procedure for biomechanical measurements was presented in a previous study.[20–22] To summarize, the cross-sectional area and width of the middle part of the harvested supraspinatus tendon were measured using a Digimatic Micrometer (MDC-25SB; Mitutoyo Co., Kanagawa, Japan).[21,23] The harvested samples were fixed in a universal testing machine (OTT-03; Oriental TM, Siheung, South Korea) along the anatomical direction and tested with a 20 kg load cell at a rate of 10 mm/min load to failure, mode of failure (insertional tear or mid substance tear) and ultimate stress parameters were measured (Figure 2(b)). An insertional tear suggests relatively weak tendon-bone healing, and a mid-substance tear suggests strong tendon-bone healing.[21]

Histological analysis

All specimens from each group were histologically analyzed to determine the extent of regeneration. First, the left shoulder of each rat was harvested. Specimens were fixed in neutral buffered 10% formalin (pH 7.4) and paraffin blocks were made. Those were cut into 4-lm thick sections and then deparaffinized and rehydrated.[24] Second, sample slides were randomly selected and stained with hematoxylin and eosin (H&E), masson's trichrome, and picosirius red. The analyses were performed by two investigators who were blinded to the different animal groups. The whole slide was used for the assessment of areas of increased cellularity and vascularity, proportion of collagen fibers, and level of maturation of the tendon-to-bone structure. The scored items included (1) continuity of collagen fiber, (2) orientation of collagen fiber, (3) density of collagen fiber, (4) maturation of the tendon-to-bone interface structure, (5) vascularity, and (6) cellularity. The histological findings for each of these items were graded semi-quantitatively into four stages (grade 0, 1, 2, and 3), wherein 0 indicated the poorest ruptured tendon appearance, one indicated poorer appearance, two indicated better appearance, and three indicated noticeably regenerated appearance, respectively. With regard to the collagen fiber continuity and parallel collagen fiber orientation items, we divided their stages using a percentage value: present at 1/4 proportion (grade 0), 1/4–1/2 proportion (grade 1), 1/2–3/4 proportion (grade 2), and 3/4 proportion (grade 3).[20,25] Collagen fiber density was graded as very loose (grade 0), loose (grade 1), dense (grade 2), or very dense (grade 3).[20,25] Each tissue slide was photographed under a microscope (Leica DM IL LED; Leica Microsystems, Wetzlar, Germany) using the LAS V4.8 software (Leica Microsystems) imaging system. Three observations were made at the rotator cuff tissue at the same location and area at ×100 magnification.[20] All images were obtained with the same illumination and magnification parameters. After a photomicrograph was captured, 8-bit digitization was performed by the ImageJ software.

Statistical analysis

All statistics were analyzed using SPSS 12.0 software (SPSS Inc. Chicago, IL, USA), and statistical significance was set to p-value \ 0.05. Chi-Square test, followed by t test, was used to evaluate the biomechanical and histological

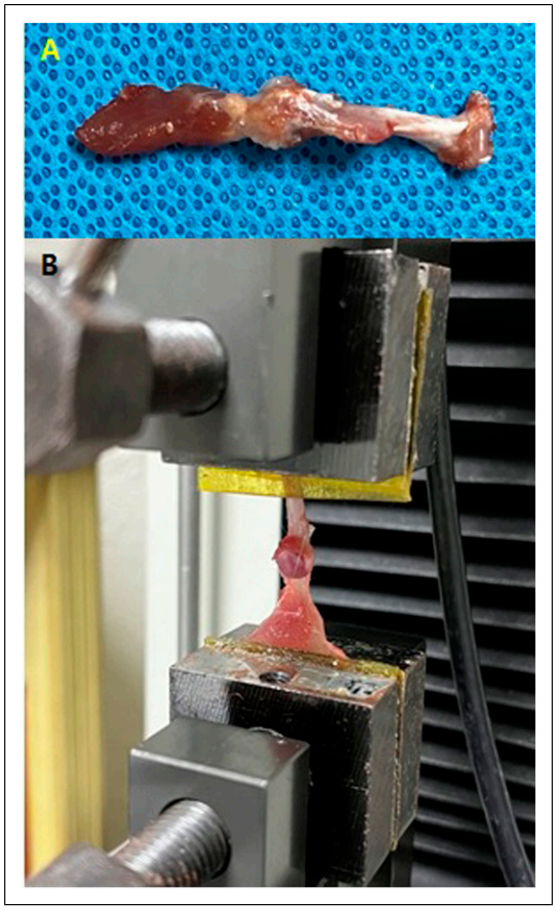

Figure 2. Biomechanical evaluation. (A) Sample harvest of the reattachment SS tendon. (B) Biomechanical test machine for measurements of load to failure, ultimate stress, and elongation.

differences between groups. Data are presented as the mean and standard deviation.

Results

Biomechanical evaluation

Visual inspection of all samples confirmed that the supraspinatus tendon-bone repair was not completely separated. (Figure 2(a)) In the biomechanical analysis, there was no significant difference in load-to-failure (group-C: 0.61 ± 0.32 N, group-aspirin: 0.74 ± 0.91 N; $p = .697$) and ultimate stress (group-C: 0.05 ± 0.01 MPa, group-aspirin: 0.29 ± 0.43 MPa; $p = .095$). For the elongation (group-C: 222.62 ± 57.98%, group-aspirin: 194.75 ± 75.16%; $p = .028$), group-aspirin confirmed a lower elongation level than group-C (Table 1).

Histological evaluation

Histologically, group-aspirin showed organized bone tendon interface structure with higher collagen fiber density (group-C: 1.60 ± 0.52, group-aspirin: 2.60 ± 0.52, $p = .001$) and vascularity (group-C: 1.00 ± 0.47, group-aspirin: 2.20 ± 0.63, $p = .001$) than the group-C (Table 2). However, there were no significant differences in the collagen fiber continuity (group-C: 1.40 ± 0.70, group-aspirin: 2.10 ± 0.74, $p = .052$), collagen fiber orientation (group-C: 1.40 ± 0.97, group-aspirin: 2.10 ± 0.74, $p = .089$), maturation of the tendon-to-bone interface structure (group-C: 1.60 ± 0.70, group-aspirin: 2.10 ± 0.74, $p = .165$), and cellularity (group-C: 1.08 ± 0.79, group-aspirin: 2.20 ± 0.63, $p = .280$) between the two groups (Table 2). In summary, there was no biomechanical improvement effect by aspirin, but histological improvement effects such as collagen fiber density and vascularity were confirmed (Figures 3 and 4).

Discussion

We evaluated the biomechanical and histological effects of aspirin at the supraspinatus tendon-to-bone interface on the repairing of RCT through biomechanical and histological analyses in a rat model. After 8 weeks surgery, biomechanical evaluation did not show a significant difference between the two groups. In the group-C, all types of failure occurred at the tendon-bone interface.

We identified increased histological properties of aspirin in a RCT rat models. Eight weeks postoperatively, the group-aspirin showed significantly improved collagen fiber density and vascularity compared with the control group. The semiquantitative evaluation also showed higher scores in the group-aspirin than in the control group. These results indicates that aspirin can induce collagen formation and promote vascularity. Previous studies have shown that the use of aspirin in the early stages of tendon injury reduces the expression of pro-inflammatory cytokines and promotes the increase of anti-inflammatory cytokines through regulation of the JNK/STAT-3 signaling pathway, producing an anti-inflammatory effect.[13] This reduction in inflammation can promote the growth of fibroblasts, which can increase collagen synthesis and promote angiogenesis in tendon regeneration.[13–15] The current results found that early use of aspirin after tendon repair surgery increased collagen density and improved vascularity at the tendon-bone interface. In summary, we strongly advocate that the use of aspirin early in tendon repair can be an effective treatment to promote healing at the tendon-bone interface by improving collagen biosynthesis and vascularity through inhibition of the inflammatory response.

As a representative NSAID, aspirin is widely accepted as a treatment for tendinopathy or ruptured tendon healing because of its anti-inflammatory and pain relieving effects in clinical practice.[15] Previous studies have shown that aspirin promotes tendon healing through anti-inflammation and inhibition of scar formation in injured tendon healing.[13] In addition, aspirin induces tenogenic differentiation of

Table 1. Comparison of the biomechanical characteristics.

	Group-C	Group-aspirin	*p*-value
Cross-sectional area, mm^2	12.57 ± 4.02	2.88 ± 1.20	0.000[a]
Load-to-failure, N	0.61 ± 0.32	0.74 ± 0.91	0.679
Ultimate stress, MPa	0.05 ± 0.01	0.29 ± 0.43	0.095
Elongation, %	222.62 ± 57.98	194.75 ± 75.16	0.028[a]

Group-C, supraspinatus repair only; Group-aspirin, SS tendon repair with aspirin injection.
[a]Statistically significant. Values expressed as mean ± standard deviation.

Table 2. Scoring of findings on histological analysis.

	Group-C	Group-aspirin	*p*-value
Collagen fiber continuity	1.40 ± 0.70	2.10 ± 0.74	0.052
Collagen fiber orientation	1.40 ± 0.97	2.10 ± 0.74	0.089
Collagen fiber density	1.60 ± 0.52	2.60 ± 0.52	0.001[a]
Maturation of the tendon-to-bone interface structure	1.60 ± 0.70	2.10 ± 0.74	0.165
Vascularity	1.00 ± 0.47	2.20 ± 0.63	0.001[a]
Cellularity	1.08 ± 0.79	2.20 ± 0.63	0.280
Total score	8.80 ± 2.30	13.3 ± 2.36	0.001[a]

[a]Statistically significant. Values are expressed as mean ± standard deviation.

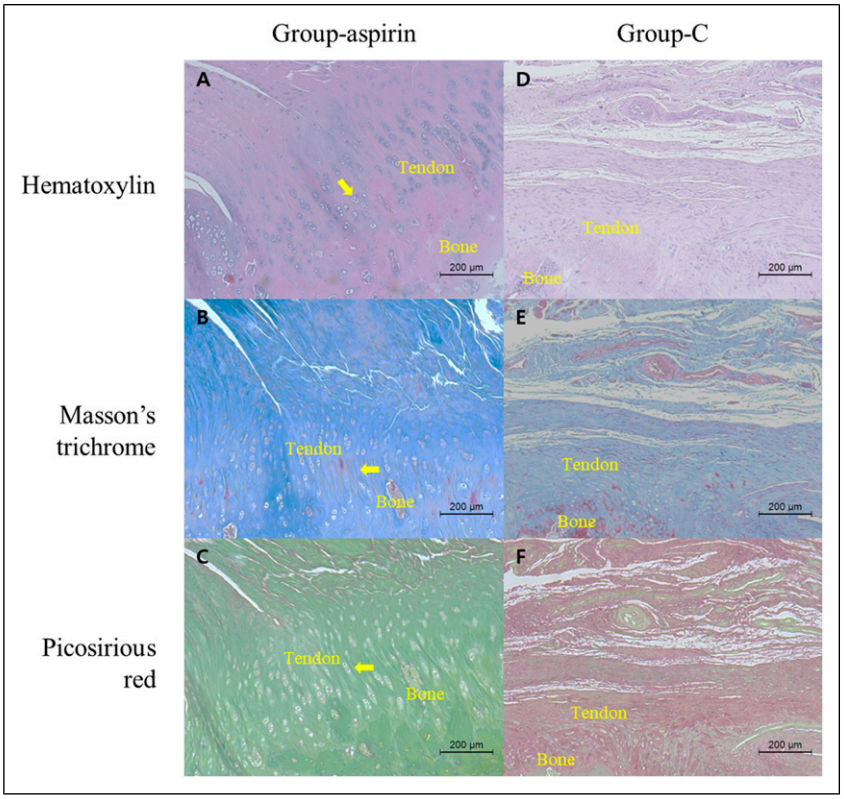

Figure 3. Histological evaluation of the SS tendon-to-bone interface. Group-aspirin: (A), (B), (C) and Group-C: (D), (E), (F) The group-aspirinshows more organized tendon-to-bone interface structures (yellow arrows) with higher collagen fiber density and vascularity than the group-C. All images by ×100 magnification.

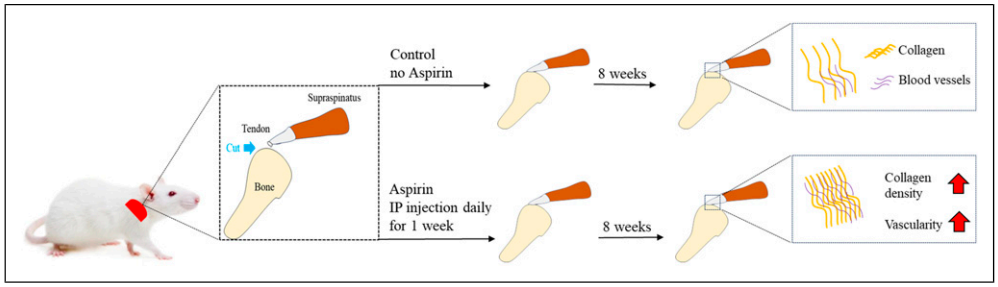

Figure 4. Macroscopic overview of aspirin-induced tendon-to-bone interface histological healing. Systemic aspirin treatment in acute rotator cuff tears increases collagen density and vascularity at the tendon-to-bone interface.

TSCs to promote tendinopathy healing, and it is known that the process regulates the GDF7/Smad1/5 signaling pathway.[15] GDF is a member of the TGF-beta superfamily, and it is known from previous reports that a null mutation of GDF6 causes a significantly lower level of tail tendon collagen content.[26] It is a report implying the important role of GDF6 in tendon matrix modeling, and it has also been reported that GDF7 can induce tenogenesis of bone marrow mesenchymal stem cell.[27] Aspirin increased the expression of GDF7/11, and increased GDF7 was found to play an important role in tenogenic differentiation in TSCs.[15] The increased collagen density and vascularity in our results suggest an effect of aspirin on promoting early tendon matrix healing. We conclude that the application of aspirin after rotator cuff repair can promote the tenogenic differentiation of TSCs in the injured tendon and thereby increase collagen density and vascularity. However, detailed mechanism studies of the increase in collagen organization and vascularity are still needed.

It's widely accepted that tendon-to-bone healing failures often result from the inability of disorganized fibrous scar tissue to provide adequate tensile strength.[28] However, appropriate fibrosis and scar formation are crucial for wound healing, closure, and infection prevention.[29,30] The improper accumulation of extracellular matrix (ECM) in scar tissue following tendon injury can cause a poor and delayed healing process, leading to inferior tissue quality.[29] The ECM in fibrotic scar tissue plays a vital role in tissue morphogenesis, differentiation, and homeostasis.[13] A previous study showed that aspirin reduces the expression of ECM degradation-related enzyme MMP-3 and lowers ECM secretion by inhibiting TSCs, thus preventing excessive ECM accumulation, excessive scar formation, and ultimately improving tendon healing.[13]

Nevertheless, this study has some limitations. First, this study is limited to non-clinical, animal studies. Because of the apparent anatomical differences between humans and mice and differences in wound and healing responses, sufficient studies are needed before aspirin can be used in humans. This study showed that the improved histological properties in tendon-to-bone healing without any signs of toxicity in vitro and in vivo. Although it is a suitable material candidate for application to rotator cuff patients from a clinical point of view, the following studies are needed for adverse reactions and efficacy in humans, including ethical issues, before application to humans. Second, it is difficult to sufficiently measure the toxicity and other side effects of aspirin within an evaluation period of 8 weeks. Therefore, it is necessary to confirm by extending the study period. Third, this study did not confirm that it promotes TSCs differentiation by the previously confirmed GDF7-mediated Smad1/5 signaling pathway. Therefore, in further study, it is necessary to confirm the regulation of the Smad1/5 signaling pathway by aspirin, and to confirm that TSCs differentiation is promoted accordingly.

These limitations should be addressed in subsequent studies. Despite these limitations, this aspirin has various advantages and can function as an amplifying agent for the mechanical and biological factors involved in the healing of rotator cuff tears.

Conclusion

In this study, we report for the first time that there was no biomechanical improvement effect of aspirin compared to the control group in a rotator cuff tear rat model, however, that it can improve collagen fiber density and vascularity in histological evaluation. These results suggest that aspirin can be an effective drug for improving tendon-to-bone structure healing in rotator cuff tear.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This

work was supported by the the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (NRF-2022R1A2C1005374).

Ethical statement

Ethical approval

The study was approved by the Ethics Committee of Kyunpook National University University (approval no. 2022-0440-2). All methods were conducted in accordance with the relevant guidelines and regulations.

IACUC information

Kyungpook National University Institutional Animal Care and Use Committee IACUC NO: KNU 2023-0111.

ORCID iDs

Hyun Joo Lee https://orcid.org/0000-0003-2837-3434
Eugene J Park https://orcid.org/0000-0002-3974-9460

References

1. Lorbach O, Baums MH, Kostuj T, et al. Advances in biology and mechanics of rotator cuff repair. *Knee Surg Sports Traumatol Arthrosc* 2015; 23: 530–541.
2. Nho SJ, Brown BS, Lyman S, et al. Prospective analysis of arthroscopic rotator cuff repair: prognostic factors affecting clinical and ultrasound outcome. *J Shoulder Elbow Surg* 2009; 18: 13–20.
3. Yamamoto A, Takagishi K, Osawa T, et al. Prevalence and risk factors of a rotator cuff tear in the general population. *J Shoulder Elbow Surg* 2010; 19: 116–120.
4. Bartolozzi A, Andreychik D and Ahmad S. Determinants of outcome in the treatment of rotator cuff disease. *Clin Orthop Relat Res* 1994; 308: 90–97.
5. Radhakrishnan R, Goh J and Tan AHC. Partial thickness rotator cuff tears: a review of current literature on evaluation and management. *Clin Shoulder Elb* 2024; 27(1): 79–87.
6. Cofield R. Subscapular muscle transposition for repair of chronic rotator cuff tears. *Surg Gynecol Obstet* 1982; 154: 667–672.
7. Di Benedetto P, Mancuso F, Tosolini L, et al. Treatment options for massive rotator cuff tears: a narrative review. *Acta Biomed* 2021; 92: e2021026.
8. Park JH, Oh KS, Kim TM, et al. Effect of smoking on healing failure after rotator cuff repair. *Am J Sports Med* 2018; 46: 2960–2968.
9. Wang PW and Jo CH. Prognostic factors affecting structural integrity after arthroscopic rotator cuff repair: a clinical and histological study. *Clin Shoulder Elb* 2023; 26: 10–19.
10. Seo S-J, Park J-Y, Park H-J, et al. Protocatechuic acid impacts rotator cuff healing and reduces fatty degeneration in a chronic rotator cuff tear model in rats. *Clin Shoulder Elb* 2022; 25: 5–14.
11. Park HB, Gwark JY and Na J-B. Risk factors of chronic subscapularis tendon tear. *Clin Shoulder Elb* 2022; 25: 257–264.
12. Zafarmand SS, Karimi-Haghighi S, Salehi MS, et al. Aspirin impacts on stem cells: implications for therapeutic targets. *Tissue Cell* 2022; 74: 101707.
13. Wang Y, He G, Tang H, et al. Aspirin inhibits inflammation and scar formation in the injury tendon healing through regulating jnk/stat-3 signalling pathway. *Cell Prolif* 2019; 52: e12650.
14. Wang Y, He G, Wang F, et al. Aspirin inhibits adipogenesis of tendon stem cells and lipids accumulation in rat injury tendon through regulating pten/pi3k/akt signalling. *J Cell Mol Med* 2019; 23: 7535–7544.
15. Wang Y, He G, Tang H, et al. Aspirin promotes tenogenic differentiation of tendon stem cells and facilitates tendinopathy healing through regulating the gdf7/smad1/5 signaling pathway. *J Cell Physiol* 2020; 235: 4778–4789.
16. Wang Y, Tang H, He G, et al. High concentration of aspirin induces apoptosis in rat tendon stem cells via inhibition of the wnt/β-catenin pathway. *Cell Physiol Biochem* 2018; 50: 2046–2059.
17. Sözlü U, Başar S and Kanatlı U. Scapular muscle endurance, shoulder pain, and functionality in patients with rotator-cuff-related shoulder pain: a matched, case-control study. *Clin Shoulder Elb* 2024; 27(1): 52–58.
18. Oh JH, Seo HJ, Lee Y-H, et al. Do selective cox-2 inhibitors affect pain control and healing after arthroscopic rotator cuff repair? A preliminary study. *Am J Sports Med* 2018; 46: 679–686.
19. Lu Y, Li Y, Li FL, et al. Do different cyclooxygenase inhibitors impair rotator cuff healing in a rabbit model? *Chin Med J* 2015; 128: 2354–2359.
20. Yoon JP, Yoon JW, Kim HM, et al. Selective serotonin reuptake inhibitor promotes bone-tendon interface healing in a rotator cuff tear rat model. *Tissue Eng Regen Med* 2022; 19: 853–860.
21. Yoon JP, Chung SW, Jung JW, et al. Is a local administration of parathyroid hormone effective to tendon-to-bone healing in a rat rotator cuff repair model? *J Orthop Res* 2020; 38: 82–91.
22. Eshima K, Ohzono H, Gotoh M, et al. Effect of suprascapular nerve injury on muscle and regenerated enthesis in a rat rotator cuff tear model. *Clin Shoulder Elb* 2023; 26: 131–139.
23. Trudel G, Ramachandran N, Ryan SE, et al. Supraspinatus tendon repair into a bony trough in the rabbit: mechanical restoration and correlative imaging. *J Orthop Res* 2010; 28: 710–715.
24. Wang H, Rong X, Yang L, et al. Advances in stem cell therapies for rotator cuff injuries. *Front Bioeng Biotechnol* 2022; 10: 866195.

25. Yoon JP, Kim DH, Min SG, et al. Effects of a graphene oxide-alginate sheet scaffold on rotator cuff tendon healing in a rat model. *J Orthop Surg* 2022; 30: 10225536221125950.
26. Mikic B, Rossmeier K and Bierwert L. Identification of a tendon phenotype in gdf6 deficient mice. *Anat Rec* 2009; 292: 396–400.
27. Hou Y, Ni M, Lin S, et al. Tenomodulin highly expressing mscs as a better cell source for tendon injury healing. *Oncotarget* 2017; 8: 77424–77435.
28. Lei T, Zhang T, Ju W, et al. Biomimetic strategies for tendon/ligament-to-bone interface regeneration. *Bioact Mater* 2021; 6: 2491–2510.
29. Lui PPY, Cheuk YC, Lee YW, et al. Ectopic chondro-ossification and erroneous extracellular matrix deposition in a tendon window injury model. *J Orthop Res* 2012; 30: 37–46.
30. Giordano JR, Klein B, Hershfeld B, et al. A review of chronic pectoralis major tears: what options are available? *Clin Shoulder Elb* 2023; 26: 330–339.