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SYMPOSIUM: SURGERY AND SCIENCE OF THE ROTATOR CUFF

# The Detrimental Effects of Systemic Ibuprofen Delivery on Tendon Healing Are Time-Dependent

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**Abstract**

*Background* Current clinical treatment after tendon repairs often includes prescribing NSAIDs to limit pain and inflammation. The negative influence of NSAIDs on bone repair is well documented, but their effects on tendon healing are less clear. While NSAIDs may be detrimental to early tendon healing, some evidence suggests that they may improve healing if administered later in the repair process.

*Questions/purposes* We asked whether the biomechanical and histologic effects of systemic ibuprofen administration on tendon healing are influenced by either immediate or delayed drug administration.

*Methods* After bilateral supraspinatus detachment and repair surgeries, rats were divided into groups and given ibuprofen orally for either Days 0 to 7 (early) or Days 8 to 14 (delayed) after surgery; a control group did not receive ibuprofen. Healing was evaluated at 1, 2, and 4 weeks postsurgery through biomechanical testing and histologic assessment.

*Results* Biomechanical evaluation resulted in decreased stiffness and modulus at 4 weeks postsurgery for early ibuprofen delivery (mean ± SD [95% CI]: 10.8 ± 6.4 N/mm [6.7–14.8] and 8.9 ± 5.9 MPa [5.4–12.3]) when compared to control repair (20.4 ± 8.6 N/mm [16.3–24.5] and 15.7 ± 7.5 MPa [12.3–19.2]) ($p = 0.003$ and 0.013); however, there were no differences between the delayed ibuprofen group (18.1 ± 7.4 N/mm [14.2–22.1] and 11.5 ± 5.6 MPa [8.2–14.9]) and the control group. Histology confirmed mechanical results with reduced fiber reorganization over time in the early ibuprofen group.

*Conclusions* Early administration of ibuprofen in the postoperative period was detrimental to tendon healing, while delayed administration did not affect tendon healing.

*Clinical Relevance* Historically, clinicians have often prescribed ibuprofen after tendon repair, but this study suggests that the timing of ibuprofen administration is critical to adequate tendon healing. This research

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Each author certifies that his or her institution approved the animal protocol for this investigation and that all investigations were conducted in conformity with ethical principles of research.
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necessitates future clinical studies investigating the use of ibuprofen for pain control after rotator cuff repair and other tendon injuries.

## Introduction

Annually, more than 28 million patients in the United States experience a tendon or ligament injury [7]. Restoration of function after tendon damage stemming from injury, overuse, or degenerative disease is largely dependent on the reestablishment of the muscle-tendon-bone connection with minimal scarring between the tendon and its surrounding tissues [16, 18]. Current clinical treatment protocols after tendon repair often include NSAIDs, chiefly for their pain-relieving effects, with a secondary indication in their limitation of inflammation [20]. NSAIDs facilitate rehabilitation by limiting pain and may also reduce the cross-sectional area of a tendon repair through decreased fibrosis (an effect that might be beneficial in flexor tendon repair in the hand, where thickening of a healing tendon, and associated difficulty traversing the pulley system, might be problematic) [26].

While NSAIDs are commonly prescribed for musculoskeletal injuries, recent research has highlighted detrimental effects of NSAIDs on healing tissues [4]. The negative influence of NSAIDs on bone metabolism and fracture healing has been well documented in experimental studies for a number of drugs [2, 11, 19, 25]. However, the effects of NSAIDs on tendon healing are not as well described [5, 8, 33]. In vitro studies have demonstrated that NSAIDs may inhibit tendon cell migration and proliferation—processes that are critical during the initial response to tendon injury [31, 32]. In addition, studies have shown that NSAIDS inhibit tendon-to-bone healing in a rat rotator cuff model via inhibition of the formation and maturation of collagen at the tendon insertion site [6].

Conversely, evidence suggests that NSAIDs may improve healing if administered later in the healing process. Indomethacin has been shown to decrease prostaglandin release and DNA synthesis and increase protein synthesis in human tendon fibroblasts [1], suggesting that it might have a negative effect on tendon healing in the early proliferative phase but might be beneficial in the remodeling phase. In addition, one study tended to confirm this hypothesis in vivo in the rat Achilles tendon, using the cyclooxygenase (COX)-2-specific inhibitor parecoxib [33]. Despite these intriguing short-term findings, more extensive mechanical and histologic evaluation is necessary to confirm and evaluate this preliminary finding and to inform clinical practice.

Therefore, we evaluated the biomechanical and histologic effects of systemic NSAID administration on tendon healing when delivered immediately (for only the first week after surgery) or in a delayed fashion (for only the second week after surgery) when compared to no NSAID administration. Specifically, we used a commonly prescribed medication, ibuprofen, in our well-established rat rotator cuff model of supraspinatus tendon healing [12, 14, 29]. We hypothesized that early administration would inhibit rotator cuff healing, resulting in decreased mechanical properties and reduced tissue organization, while late administration would improve rotator cuff healing, resulting in increased mechanical properties and tissue organization. In addition, we hypothesized that fiber organization would increase and cellularity would decrease over time after surgery in the control group and the delayed group, but these changes would not be present in the early ibuprofen group.

## Materials and Methods

This study was approved by the University of Pennsylvania Institute for Animal Care and Use Committee (Protocol 804336). Sixty-five male Sprague-Dawley rats (obtained at 400–450 g) were randomly assigned to one of three groups (Fig. 1): (1) control repair, (2) repair with early systemic ibuprofen administration (early), or (3) repair with delayed systemic ibuprofen administration (delayed). Rats designated for either the early or delayed group were trained to drink fluid from a 1-mL needleless syringe twice a day for 3 to 4 days before surgery. Animals did not need to be restrained for this task as they willingly drank fluid from the syringe after their training period. All animals then underwent bilateral supraspinatus detachment and repair surgeries as described previously in detail [3, 27]. Buprenorphine was administered subcutaneously to all animals at a dose of 0.05 mg/kg immediately before surgery and then every 8 to 12 hours for the next 2 days. In addition, rats designated for the early or delayed group were given liquid ibuprofen (FDA approved) orally via syringe at a dose of 20 mg/kg every 8 to 12 hours. This dose was based on the pharmacokinetics of ibuprofen in the rat, such that the dose would maintain a moderate concentration of plasma ibuprofen for up to 12 hours after administration [24]. The early and delayed groups received ibuprofen on Days 0 to 7 and Days 8 to 14 after surgery, respectively. Rats were allowed normal cage activity and were euthanized at 1 (early and control groups only), 2, or 4 weeks postsurgery (Fig. 1). Sample sizes were based on power analyses using previous supraspinatus repair data that showed a minimum of 12 specimens would be needed to detect mechanical changes and a minimum of four

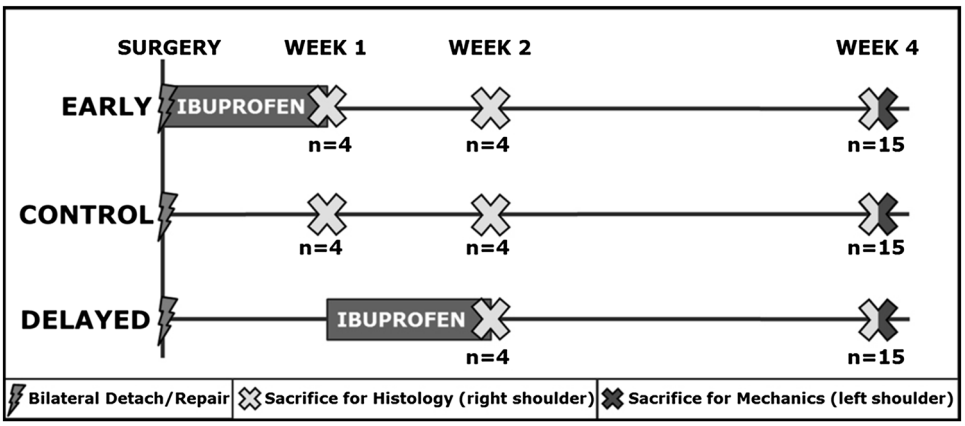


**Fig. 1** The overall study design involved three groups: early ibuprofen administration (on Days 0–7 after surgery), control repair, and delayed ibuprofen administration (on Days 8–14 after surgery). Animals were sacrificed at 1, 2, or 4 weeks after bilateral supraspinatus tendon detachment and repair surgeries and shoulders were allotted to histologic (1, 2, 4 weeks) or mechanical evaluation (4 weeks only).

specimens to detect histologic changes. One shoulder of each animal was dissected immediately after sacrifice for histologic preparation and the other was frozen and used for mechanical evaluation.

For biomechanical testing, supraspinatus tendons at 4 weeks postsurgery (n = 15 tendons/group) were dissected free from all connective tissue, leaving the insertion to the humerus intact. Verhoeff stain lines were placed on the tendon at 1, 2, 4, and 8 mm from the insertion site (determined visually) for measurement of optical strain. Tendon cross-sectional area was measured using a custom laser-based device. The tendon was fixed between two layers of sandpaper using a cyanoacrylate adhesive and clamped using custom grips. The humeral diaphysis was potted in polymethylmethacrylate and placed in a base fixture. Specimens were submerged in a 37° C phosphate-buffered saline bath and tensile tested using an Instron 5543 mechanical test frame (Instron Corp, Norwood MA, USA) using a protocol described previously [3, 21]. Briefly, tendons were subjected to 10 cycles of preconditioning between 0.1 and 0.5 N to provide consistent strain history between specimens and then allowed to return to equilibrium over 300 seconds. A stress relaxation ramp to 5% strain was then performed at a rate of 5%/second, followed by a 600-second relaxation. Finally, tendons were returned to their initial gauge length for 60 seconds and then subjected to a ramp to failure at 0.3%/second. Percent relaxation was calculated as the peak load of the initial strain minus the equilibrium load after 10 minutes of relaxation divided by the peak load. Maximum stress was calculated as the maximum load of the ramp to failure divided by the cross-sectional area. Displacement was tracked optically using custom MATLAB® software (Mathworks Inc, Natick, MA, USA). Briefly, the positions of a pair of stain lines were tracked during the ramp to failure portion of the mechanical test based on texture correlation. The change in length between the stain line pair was averaged across the width of the specimen to determine tissue displacement. Optical stiffness was then calculated from the slope in the linear region of the load-tissue displacement curve. Finally, optical stiffness was multiplied by the specimen's initial length and divided by the cross-sectional area to determine optical modulus.

For histologic assessment, four supraspinatus tendons per time point (1, 2, and 4 weeks) were grossly harvested from the shoulder, leaving the muscle and bony insertions intact. Specimens were fixed, decalcified, and processed for paraffin embedding using standard techniques. Coronal sections were cut to 7-μm thickness and stained with hematoxylin and eosin to visualize cellularity and cell shape and alcian blue and picrosirius red for collagen organization. A single image at x20 magnification was obtained for each specimen at the insertion site of the tendon with close proximity to the bony insertion. The images were then evaluated using BIOQUANT software (BIOQUANT Image Analysis Corp, Heidelberg, Germany) for cellularity and cell shape. Briefly, cell nuclei were selected based on threshold values for the purple staining of nuclei with hematoxylin and eosin stain. Cellularity was calculated as a nuclei density per area of region analyzed. Cell shape was measured as the ratio of the nucleus area to the area of a circle with an identical perimeter. Effectively, this is a measurement of the roundness of the nuclei on a scale from 0 (straight line) to 1 (perfect circle).

Finally, fiber organization in the region of interest was quantitatively evaluated using custom software as described previously [13, 14, 28]. Briefly, specimens were placed on a polarized light microscope stage between an analyzer and a polarizer, which were crossed. Grayscale images were taken at 5° increments as the analyzer and polarizer were simultaneously rotated through 90°. The images were then analyzed using custom-designed MATLAB® software. A grid of points was analyzed per location in each tissue section and the angle of minimum

light intensity, which indicates the orientation of the collagen, was calculated for each point. Angular orientation for all points was combined to generate a histogram for quantitative comparison. Circular SD, a measure of the spread of that distribution, was calculated and compared across groups.

The comparisons made in this study were focused to test the two main hypotheses: (1) the early group was different from the control group and (2) the delayed group was different from the control group. Therefore, parameters evaluated from the biomechanical assessment were compared using a one-way ANOVA with Dunnett's post hoc test to compare each group to the control. Histologic parameters were evaluated using a two-way ANOVA for each hypothesis with effects of time after surgery, time of ibuprofen dosing, and the interaction. If any effects were significant, post hoc tests with Bonferroni corrections were performed. For all assessments, statistical significance was set at p values of 0.05 or less. We performed statistical analyses using IBM® SPSS® Statistics Version 20 (IBM Corp, Somers, NY, USA).

## Results

At 4 weeks postsurgery, tendon stiffness and modulus of elasticity were decreased for early ibuprofen delivery (mean ± SD [95% CI]: 10.8 ± 6.4 N/mm [6.7–14.8] and 8.9 ± 5.9 MPa [5.4–12.3]) compared to control repair (20.4 ± 8.6 N/mm [16.3–24.5] and 15.7 ± 7.5 MPa [12.3–19.2]) (p = 0.003 and 0.013), while stiffness and modulus were not affected by late ibuprofen delivery (18.1 ± 7.4 N/mm [14.2–22.1] and 11.5 ± 5.6 MPa [8.2–14.9]) (Table 1). All of the specimens tested in this study failed at the insertion site or midsubstance of the tendon. Tendon cross-sectional area for either the early or delayed group was not significantly different from that for the control group (Table 1). There were also no differences in percent relaxation, maximum load, or maximum stress relative to control in either the early or delayed group (Table 1).

While there were no significant differences in the interaction of group and time in any histologic parameter, there was a significant effect of time and group in collagen fiber alignment in the two-way ANOVA (p = 0.0146 and 0.0299) (Table 2). Post hoc one-way ANOVAs over time for each group revealed a significant increase in fiber alignment (decrease in circular SD) in the control group (p = 0.0176) but not in the delayed or early groups. Post hoc tests comparing groups at each 1 week postsurgery revealed a significantly lower fiber alignment in the early group when compared to the control group (p = 0.0084), but there were no significant differences at any other time point. Despite fiber organization differences, there were no significant differences among groups or time points in cell density or cell shape.

Both ibuprofen groups had significant blood vessel formation and bleeding after surgery when compared to the control group. Qualitatively, six of the 22 histologic samples in the early and delayed groups were noted to have blood vessel formation near the insertion and in the forming scar tissue, compared to only one specimen in the control group. Documented observations at dissection (performed blinded to group) of mechanically tested specimens also confirmed that 79% of specimens in the early group had moderate hematomas at the injury site even 4 weeks after surgery, compared with 40% in the delayed group and only 29% in the control group.

## Discussion

NSAIDs are commonly administered after rotator cuff repair to relieve pain and reduce inflammation. However, evidence in both bone and tendon literature suggests that

**Table 1.** Descriptive statistics for biomechanical results

| Group | Area ($mm^2$) | Percent relaxation | Maximal load (N) | Maximal stress (MPa) | Stiffness (N/mm) | Modulus (MPa) |
|---|---|---|---|---|---|---|
| Control | 5.0 ± 1.0 (4.1–5.9) | 60 ± 19 (49–71) | 10.7 ± 3.0 (9.2–12.2) | 2.1 ± 0.8 (1.7–2.4) | 20.4 ± 8.6 (16.3–24.5) | 15.7 ± 7.5 (12.3–19.2) |
| Early | 5.0 ± 2.2 (4.1–5.9) | 55 ± 24 (44–66) | 8.6 ± 2.7 (7.1–10.1) | 1.7 ± 0.4 (1.3–2.0) | 10.8 ± 6.4 (6.7–14.8) | 8.9 ± 5.9 (5.4–12.3) |
| Delayed | 5.1 ± 1.6 (4.2–6.0) | 55 ± 17 (45–66) | 10.5 ± 2.4 (9.1–12.0) | 1.9 ± 0.6 (1.5–2.2) | 18.1 ± 7.4 (14.2–22.1) | 11.5 ± 5.6 (8.2–14.9) |
| p value (one-way ANOVA) | 0.970 | 0.728 | 0.104 | 0.271 | 0.004 | 0.024 |
| p value (one-way ANOVA with post hoc test) | | | | | | |
| Control vs early | | | | | 0.003 | 0.013 |
| Control vs delayed | | | | | 0.628 | 0.148 |

Values are expressed as mean ± SD, with 95% CI in parentheses.

**Table 2.** Descriptive statistics for histologic results

| Group | Time (weeks) | Cell density (cells/μm$^2$) | Cell shape (nucleus aspect ratio; 0 = flat, 1 = round) | Fiber alignment (circular SD [°]) |
|---|---|---|---|---|
| Control | 1 | 0.00104 ± 0.00015 (0.0008–0.0013) | 0.575 ± 0.036 (0.517–0.632) | 44.11 ± 7.60 (32.02–56.20) |
| | 2 | 0.00214 ± 0.0020 (−0.0010 to 0.005) | 0.539 ± 0.11 (0.264–0.814) | 30.39 ± 14.35 (7.559–53.23) |
| | 4 | 0.00069 ± 0.000056 (0.0005–0.0008) | 0.569 ± 0.086 (0.355–0.782) | 26.58 ± 10.84 (9.326–43.84) |
| Early | 1 | 0.00080 ± 0.00055 (−0.00007 to 0.002) | 0.636 ± 0.095 (0.485–0.786) | 31.64 ± 17.22 (4.233–59.04) |
| | 2 | 0.00231 ± 0.0017 (−0.0004 to 0.005) | 0.565 ± 0.078 (0.441–0.690) | 30.20 ± 5.15 (22.01–38.39) |
| | 4 | 0.00394 ± 0.0037 (−0.002 to 0.010) | 0.538 ± 0.085 (0.402–0.673) | 27.70 ± 9.56 (12.48–42.92) |
| Delayed | 2 | 0.00128 ± 0.00022 (0.0009–0.002) | 0.613 ± 0.048 (0.537–0.689) | 38.92 ± 10.11 (22.84–55.01) |
| | 4 | 0.00158 ± 0.0013 (0.0002–0.003) | 0.557 ± 0.081 (0.472–0.641) | 29.43 ± 9.22 (19.75–39.11) |
| p value (two-way ANOVA) | | | | |
| Time | | 0.2002 | 0.4259 | 0.0146 |
| Group | | 0.1899 | 0.7873 | 0.0299 |
| Group * time | | 0.2271 | 0.5197 | 0.0650 |
| p value (post hoc tests) | | | | |
| Control (one-way ANOVA) | | | | 0.0176 |
| Early (one-way ANOVA) | | | | 0.7960 |
| Delayed (one-way ANOVA) | | | | 0.0721 |
| 1 week (t-test) | | | | 0.0084 |
| 2 weeks (one-way ANOVA) | | | | 0.0725 |
| 4 weeks (one-way ANOVA) | | | | 0.8995 |

there may be detrimental effects of this type of drug on tissue healing. We therefore tested the hypothesis that ibuprofen is detrimental to tendon healing when delivered early during the healing process but not when delivered in a delayed fashion, and our results suggested, in this animal model, this indeed appears to be the case.

This study is not without limitations. While ibuprofen was determined to be present at the shoulder based on the increased presence of hematomas in the ibuprofen groups, the exact local dose of ibuprofen in the supraspinatus tendon is unknown. The dose in this study was chosen to maintain a constant serum ibuprofen level during the 7-day dosing period, which implies a high consumption of these drugs. While this may not be relevant to a sporadic user of NSAIDs, postsurgical regimens do often include these types of levels early after surgery. Multiple dose levels will be investigated in the future. In addition, the processing of ibuprofen in the rat may be different from that in the human. Evidence suggests that while the bound fraction of ibuprofen is less in Sprague-Dawley rats than in humans, the overall metabolic processing of this drug is very similar in these two species [22], suggesting the dosing in this study is relevant to future clinical studies. In addition, the data here indicate significant changes with administration of ibuprofen, which is a nonselective COX inhibitor. COX-2-specific inhibitors seem to have a stronger detrimental effect in fracture healing [10, 11] and patellar tendon healing [8], and further investigation into COX-1 and COX-2 expression during tendon healing is warranted. As healing may be affected by animal activity level, one limitation may be the lack of quantitative cage activity measurement. However, all animals were awake and ambulating normally within 20 minutes of the surgery and no differences in activity were observed among groups during daily monitoring of animals for the first 2 weeks after surgery. Finally, this study examined the response to ibuprofen administration after an acute injury, but injury in a chronic degenerative condition may be more clinically relevant for future studies.

The first hypothesis of this study, that delivery of ibuprofen in the period immediately after surgery would be detrimental to tendon healing, was supported based on our findings. Biomechanical results at 4 weeks postsurgery in the early group exhibited decreased stiffness and modulus when compared to the control group; histologic results tended to support this finding. Since differences in cross-sectional area

of the tissue were not found, these results suggest that the overall quality of the repair tissue was diminished and indicate an altered or delayed healing for which the mechanism is not elucidated in this study. These results are supported in the literature with other NSAIDs and other tendons, in vitro and in vivo. In primates, oral ibuprofen has been shown to decrease the tendon rupture strength of repaired extensor tendon injuries [17]. Finally, indomethacin and celecoxib have also been shown to inhibit tendon-to-bone healing in a rat rotator cuff model, and in the rat patellar tendon, celecoxib, valdecoxib, and piroxicam administration decreased healing strength at the insertion site [8]. In vitro studies have demonstrated that both celecoxib and ibuprofen inhibit tendon cell migration and proliferation—processes that are critical during the initial response to tendon injury [31, 32]. These drugs appear to inhibit the formation and maturation of collagen at the tendon insertion site, which is important for early matrix production.

Our results also suggested that the delivery of ibuprofen in a delayed fashion after surgery was not detrimental to tendon healing. Tendon mechanical properties were, for the most part, unaltered in the delayed group when compared to the control group, and, again, histologic results tended to support this finding. While early administration of NSAIDs has been well studied in the literature, there have been few studies investigating a delayed administration. In vitro, indomethacin was shown to decrease prostaglandin release and DNA synthesis and increase protein synthesis in human tendon fibroblasts [1], suggesting that it may have a negative effect on tendon healing in the early proliferative phase but be beneficial in the remodeling phase. Only one other study has investigated this hypothesis specifically in vivo [33]. Intramuscular injections of parecoxib were administered for on either Days 1 to 5 Days 6 to 14 after surgery. After 2 weeks, early treatment resulted in decreased mechanical properties, while late treatment resulted in increased properties. Our results do not suggest an improved mechanical response with delayed ibuprofen administration, as in that study, but instead support the lack of a detrimental effect. However, the study of Virchenko et al. [33] involved a COX-2-specific inhibitor, which may have a stronger effect (as evidenced by other studies [8, 11]), and the drug was delivered directly to the injured area, which may result in higher dosing levels than oral administration. Our study is a more extensive mechanical and histologic evaluation at a later time point, which confirms no detrimental effect of delayed ibuprofen administration.

Our results also suggest that fiber reorganization after supraspinatus repair surgery is altered with administration of ibuprofen. Organization was decreased initially after surgery but increased over healing time in the control group, as has been seen in several previous studies [23, 29, 34]. This phenomenon was not seen in the early group, which when compared to the control had increased fiber organization at 1 week postsurgery that did not change over time. This could suggest either that structural reorganization of the healing tendon is altered due to early ibuprofen administration or that earlier matrix degradation and production are altered by ibuprofen administration. NSAIDs have been shown to alter both cell motility and tenocyte matrix metalloproteinase expression in vitro [30, 31], lending support to these ideas. Interestingly, the delayed group did exhibit a recovery of fiber alignment with increased postsurgery time, but this process seemed delayed as there was no significant difference between 1 and 2 weeks postsurgery, as in the control. These results suggest there may be a critical administration period of NSAIDs to produce detrimental mechanical and structural effects and that more evidence is necessary to determine the biologic mechanism.

We investigated the administration of a clinically relevant drug and dose in a well-established rat rotator cuff model of injury. Our findings demonstrate that use of NSAIDs, specifically ibuprofen, in the immediate postoperative period may be detrimental to tendon healing, based on mechanical properties and scar tissue integrity, even several weeks after administration. In addition to informing future clinical studies focused on postsurgery drug protocols, this work could have implications for individuals who self-medicate after smaller-level injuries and for overuse or repetitive fatigue injuries that are thought to result from accumulation of low-level damage in the tendon [15]. Recent surveys of football players show that abuse of NSAIDs is very common, noting that about 96% of collegiate players had or were using NSAIDs [15] and that about 15% of high school users considered themselves daily users [9]. Based on our study, abuse of this widely available drug could exacerbate or accelerate the progression of small-level injuries, and further study in this area is necessary to confirm these effects in humans. Interestingly, our study confirms that a delayed use of NSAIDs is not detrimental to tendon healing at later time points. Future studies will investigate various limitations of this study, specifically the effects of local administration versus systemic administration, ibuprofen administration on degenerative tendons, and nonselective versus COX-2-specific NSAIDs on tendon healing.

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