ORIGINAL PAPER/PŮVODNÍ PRÁCE

Impact of Treadmill Running Intensity on Lubricin Levels in Rat Achilles Tendons

Vliv intenzity běhu na běžeckém pásu na hladiny lubricinu v Achillových šlachách potkanů

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This research was funded by the President Foundation of Nanfang Hospital, Southern Medical University (grants No. 2020C014 and 2020B19).

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Li S-F, Song C-X, Liu S-Y, Liu W, Xu S-Y. Impact of Treadmill Running Intensity on Lubricin Levels in Rat Achilles Tendons. Acta Chir Orthop Traumatol Cech. 2026;93:111-118.

ABSTRACT

Purpose of the study

The Achilles tendon is crucial for transferring force from the calf muscles to the heel bone. Lubricin, a key glycoprotein, ensures smooth tendon gliding. This study investigated the effects of different treadmill running intensities on lubricin levels in rat Achilles tendons and explored the associated molecular mechanisms.

Material and methods

Eighteen rats were divided into three groups: Strenuous Treadmill Running (STR), Moderate Treadmill Running (MTR), and a sedentary Control group (CON). The running protocols were conducted over eight weeks. Post-intervention, tendon samples were analyzed for histological changes (collagen fiber integrity and cell count), lubricin levels, and the expression of TGF-β1 (a growth factor involved in tendon healing) and IL-1 (a pro-inflammatory cytokine).

Results

The STR group exhibited significantly greater collagen fiber damage compared to the other groups. In contrast, the MTR group showed higher cell proliferation, elevated lubricin levels, and increased TGF-β1 expression. The STR group had reduced lubricin levels, likely due to elevated IL-1 expression.

Discussion

MTR enhances tendon health by upregulating TGF-β1, increasing lubricin production, and improving load transmission. Conversely, STR may promote tendon degeneration by elevating IL-1, reducing lubricin levels, and increasing the risk of tendinopathy. These findings support previous research indicating that moderate mechanical loading maintains tendon homeostasis, whereas excessive loading leads to inflammation and structural damage.

Conclusions

Moderate-intensity treadmill running boosts lubricin levels via TGF-β1 regulation, supporting tendon function, while strenuous running decreases lubricin due to IL-1 upregulation, increasing tendon injury risk. These results emphasize the importance of optimal exercise intensity in preventing tendinopathies and maintaining tendon health. The findings could guide exercise recommendations for athletes and rehabilitation programs. Future research should explore therapeutic strategies targeting the TGF-β1 and IL-1 pathways.

Key words: lubricin, TGF-β1, IL-1, Achilles tendon, treadmill running, tendinopathy.

INTRODUCTION

Lubricin is a vital mucinous glycoprotein initially discovered in the synovial fluid and has been identified as a product of synovial cells. Its primary function is to provide lubrication in the joints to safeguard cartilage surfaces (13, 16). Recent research has revealed that lubricin is also present in human and canine tendons and exhibits both anti-adhesion and lubricating properties (2, 5, 10, 14). The molecule is primarily located within fascicles and fascicular sheaths, facilitating movement between tendon fascicles and gliding against surrounding tissues. This

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indicates that lubricin plays a crucial role in lubricating the motion between fascicles in tendons, thereby enhancing tendon gliding in vitro and in vivo (6, 7, 15).

Tendons are vital in the body, as they help transfer mechanical force from muscles to bones, which is crucial for joint movement and stabilization (22). The primary structural components that enable this force transmission are collagen fibers (12, 27). These fibers are arranged in fascicles, which run straight and parallel to each other, but have periodic crimps (17, 18). When tendons transmit force, the collagen fibers allow gliding, enabling them to stretch, and the crimps to flatten. The collagen fibers recover elastically as the tendons relax, and the crimps return to their original shape (17). Lubricin, a lubricating molecule found in the fascicles and fascicular sheaths, supports tendon function by facilitating gliding between adjacent fascicles (19). Therefore, lubricin plays a critical role in enhancing the tendon loading transmission efficiency.

Furthermore, studies have shown that certain mechanical and biochemical factors can affect the lubricin level in tendons. For example, Sun et al. found that stress deprivation, caused by suspending the forepaws without weight-bearing for 21 days, decreased lubricin synthesis in canine flexor tendons (19, 20). However, Zhang et al. discovered that extracorporeal shockwave therapy increased lubricin expression in tendons and septa at low and high doses over four days (29). Furthermore, previous research has suggested that transforming growth factor-β1 (TGF-β1) and interleukin-1 (IL-1) can also affect lubricin expression in tendons (29).

Extensive research has been conducted to explore the characteristics of lubricin in the tendons. However, the influence of diverse mechanical loading conditions on lubricin remains unclear. The primary objective of this study was to scrutinize the repercussions of treadmill running at different exercise intensities on alterations in lubricin content. We aimed to enhance our understanding of the role of lubricin in Achilles tendon function and potentially account for the inconsistent occurrence of tendinopathy and tendon rupture during rigorous PA.

MATERIAL AND METHODS

Experimental animals and exercise protocols

The experimental procedures conducted to obtain tendon samples and conduct treadmill runs were thoroughly reviewed and approved by the Animal Ethics Committee of Nanfang Hospital, Southern Medical University.

Eighteen male Wistar rats, aged 12 weeks and weighing-250 g, were randomly divided into one of three groups: control (CON, n=6), moderate treadmill running (MTR, n=6), and strenuous treadmill running (STR, n=6). The study involved three separate experiments, and all rats had access to unlimited food and water throughout the study. They were kept in a temperature-controlled room at 22±1 °C with a 12:12 h light-dark cycle.

The procedures followed the established methods (25). Initially, all animals underwent treadmill running for a week at a speed of 10 m/min for 30 min per day and five days per week. After this adaptation period, rats in the MTR and STR groups were trained to run regularly for eight weeks. The MTR group ran for 60 min per day at a speed of 19 m/min with a 5° incline, while the STR group ran for 5 days per week at 27 m/min with a 10° incline. The mice in the CON group were allowed to move freely in their cages. All protocols adhered to institutional standards for proper care and use of experimental animals.

Following the treadmill experiment, the rats underwent humane euthanasia involving carbon dioxide asphyxiation and cervical dislocation. The gastrocnemius and soleus muscles were carefully dissected by removing all soft tissues, including the plantaris muscle-tendon unit. The merged tendons were then isolated by precisely cutting them at the distal end of the gastrocnemius soleus muscle belly and distally at the calcaneus insertion (27). To enable detailed histological analyses, the right Achilles tendon of each rat was preserved in a 10% buffered formalin solution. Meanwhile, The left Achilles tendon was divided into two parts, frozen and then stored at a temperature of –80 °C. One part was used for mRNA expression analysis, while the other was used for western blotting.

Hematoxylin-eosin (H&E) staining

In line with the method outlined in reference (26), H&E staining was performed. Tendons were fixed and dehydrated using ethanol and xylene in a gradient manner and then embedded in paraffin. The samples were subsequently sliced into 4-μm-thick sections. Following gradient deparaffinization and rehydration, sections were subjected to H&E staining. The resulting collagen fibril morphologies were observed using a polarized light microscope (Axioskop 40 Pol) with a 20× objective lens.

Immunohistochemistry for lubricin

To identify lubricin (16), we used established immunohistochemical methods. Sections were prepared in the same manner as for H&E staining. To eliminate endogenous peroxidase activity, the sections were treated with 3% hydrogen peroxide for 20 min, followed by antigen retrieval with protease K and blocking with goat serum. We then incubated the sections with anti-rat lubricin primary antibodies (sc-98454) (Santa Cruz Biotechnology Inc., Santa Cruz, CA, USA) overnight at 4 °C.

Afterwards, the sections were incubated with secondary antibodies (1:200; Santa Cruz Biotechnology, CA, USA) for

Table 1. **Primer sequence used in quantitative PCR**

PRIMER	FORWARD	REVERSE
GAPDH	5'-GGCACAGTCAAGGCTGAGAATG -3'	5'-ATGGTGGTGAAGACGCCAGTA-3'
TGF-β1	5'- TGCGCCTGCAGAGATTCAAG -3'	5'- TAACGCCAGGAATTGTTGCTA-3'
IL-1	5'-CTCCATGAGCTTTGTACAAGG-3'	5'-TGCTGATGTACCAGTTGGGG-3'
lubricin	5'-AGGGCGTTGCATCCAAGAA-3'	5'-ACAGTTGCAGGTGGCGTCTCTA-3'

Abbreviation: GAPDH – glyceraldehyde-3-phosphate dehydrogenase; TGF-β1 – transforming growth factor-β1; IL-1 – interleukin-1.

1 h at room temperature. The sections were developed using 3,3'-diaminobenzidine tetrahydrochloride (DAKO, Glostrup, Denmark) and counter-stained with hematoxylin. In the control group, the primary antibody was replaced with blocking solution.

All incubation times and conditions were carefully monitored to ensure comparability. Finally, we examined the sections under a Nikon H600L microscope and image analysis system in Tokyo, Japan and captured the resultant images using Image-Pro Plus software (version 6.0; Media Cybernetics, Silver Spring, MD, USA).

Western blotting

In this experiment, the Achilles tendon tissues were treated with lysis buffer containing 0.5% sodium deoxycholate, 0.5 mM phenylmethylsulfonyl fluoride, and protease inhibitors. The supernatant was obtained by centrifugation at 12,000 × g for 15 min at a temperature of 4 °C after subjecting the samples to ultrasonic processing. Next, the protein concentration in the supernatant was quantified using a NanoDrop 1000 spectrophotometer, a widely accepted method employed in research. Subsequently, 20μg of protein for each sample was separated via 12% SDS-PAGE and electrophoretically transferred onto polyvinylidene difluoride membranes. After blocking with 3% bovine serum albumin, the membranes were incubated with anti-rat lubricin antibody (1:100; Cat. No. ab175404; Abcam) for 12 h at 4 °C. The membranes were washed three times with 0.2% TBS buffer solution, followed by incubation with mouse anti-rabbit IgG-HRP secondary antibodies (1:1,000; Catalogue Number sc2357; Santa Cruz Biotechnology, Inc.) at room temperature for one hour. Protein bands were detected using Enhanced Chemiluminescence technology, specifically the Luminata™ Crescendo Western HRP Substrate (EMD Millipore, Billerica, MA, USA). A Molecular Imager® ChemiDoc™ XRS system (Bio-Rad Laboratories, Inc.) was used for detection. The protein expression of lubricin was quantified using Image-Pro Plus software (v6.0; Media Cybernetics, Rockville, MD, USA) and normalized to GAPDH.

Quantitative real-time polymerase chain reaction (qRT-PCR)

Following the manufacturer's instructions, total RNA was extracted from Achilles tendon tissues using Trizol reagent. Subsequently, the RNA was converted to cDNA using a transcription RT Kit and a standard protocol. Real-time PCR was performed on an ABI 7500 Fast system. The suggested protocol involved an initial heating step at 95 °C for 10 min, followed by 45 cycles at 95 °C for 10 s, 55 °C for 15 s, and 72 °C for 30 s. PCR primers were obtained from Bio Teke Co., Ltd. (Beijing, China); detailed information is presented in Table 1. The target gene expression level was standardized relative to the level of GAPDH. The $2\text{-}\Delta\Delta C_T$ formula was used to calculate the relative mRNA expression of TGF-β1, IL-1, and lubricin in the MTR or STR groups compared to the CON group.

Statistical methods

Statistical data are presented as the mean values and corresponding standard deviations. To compare the groups, we conducted one-way analysis of variance and used Tukey's test for post-hoc analysis. Statistical analyses used SPSS 16.0 (SPSS Inc., Chicago, IL, USA). Significance level: $p < 0.05$.

RESULTS

Histological observation

The images presented in Fig. 1 illustrate the varying collagen fibril structures observed in Achilles tendon sections across the three groups over eight weeks. Following staining with H&E, the sections were analyzed using a polarized light microscope. In both the control (CON) and moderate exercise (MTR) groups, collagen I fibers were visibly parallel, crimped, elastic, and featured a yellow stain. Conversely, the strenuous exercise (STR) group exhibited more ruptured collagen I fibers. Notably, the moderate exercise group showed decreased interfascicular friction, while the strenuous exercise group demonstrated increased interfascicular friction.

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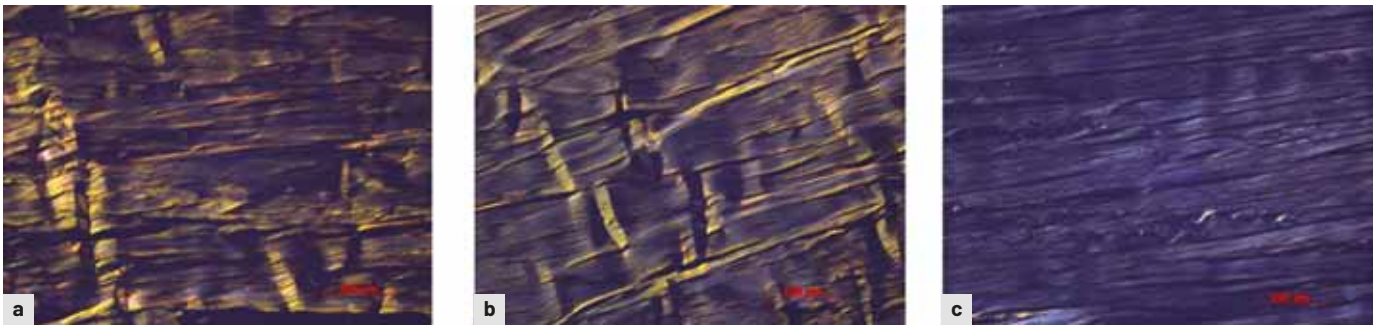


Fig. 1. **Morphologies of collagen fibrils from rat Achilles tendons stained with H&E under a polarized light microscope in CON (A), MTR (B), and STR (C) groups at eight weeks (n = 6). The yellow stain signs the type I collagen, which means stronger tendon strength, while the blue stain signs the type III collagen. The scale bar represents 100 μm.**

H&E staining

Images displaying tendon histology for H&E staining were presented for the CON (Fig. 2a), MTR (Fig. 2b), and STR (Fig. 2c) groups at the eight-week mark. Upon conducting histological analysis (Fig. 2d), it was observed that the cell density in the Achilles tendon sections notably rose in the MTR group as opposed to the CON group (p = 0.041). Conversely, it was observed that in the STR group, cell density decreased significantly compared to both the CON and MTR groups (p = 0.039 and p = 0.028, respectively).

Immunohistochemistry

The present study investigated the immunostaining of lubricin in Achilles tendon sections from three groups, namely

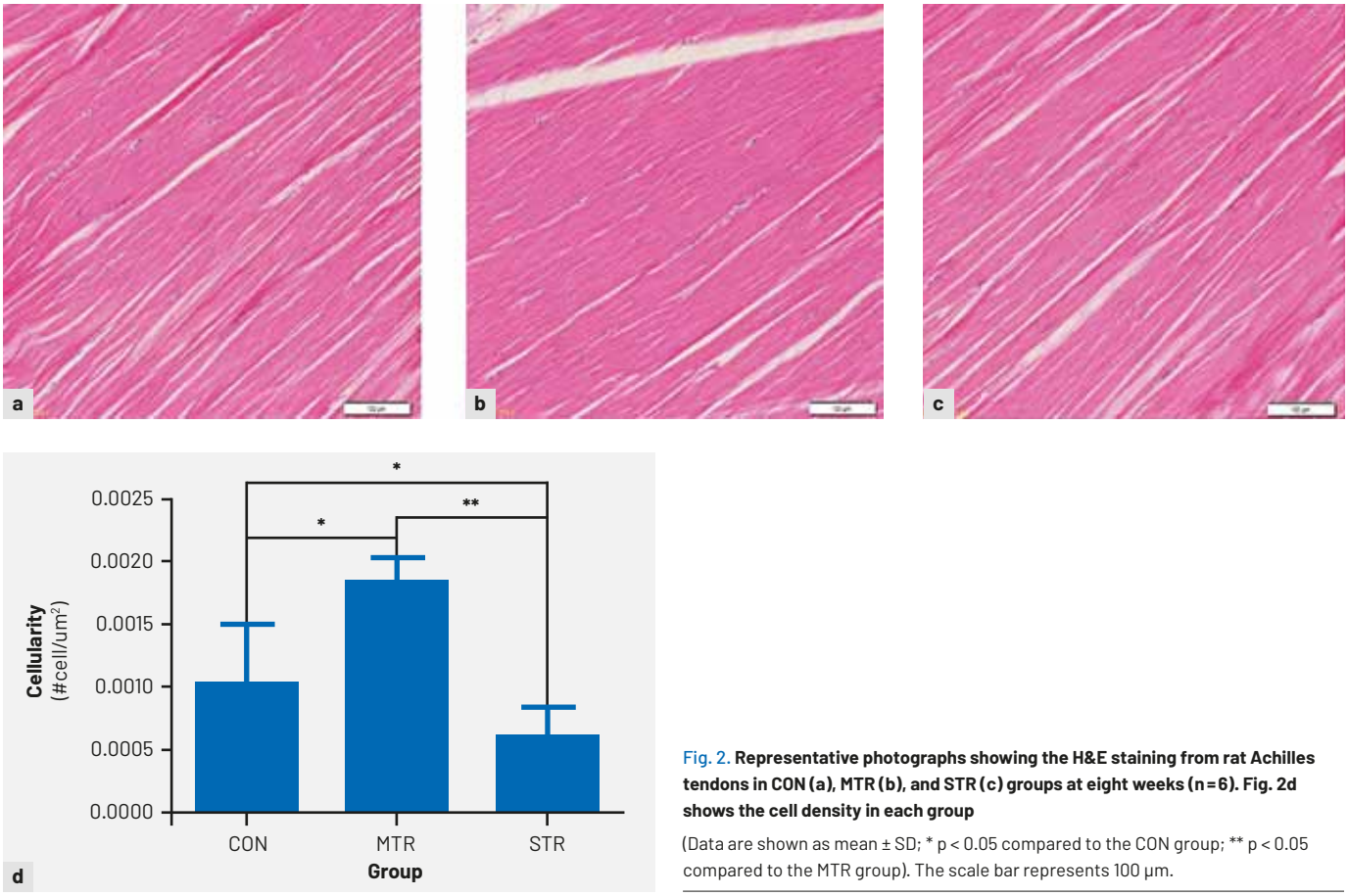
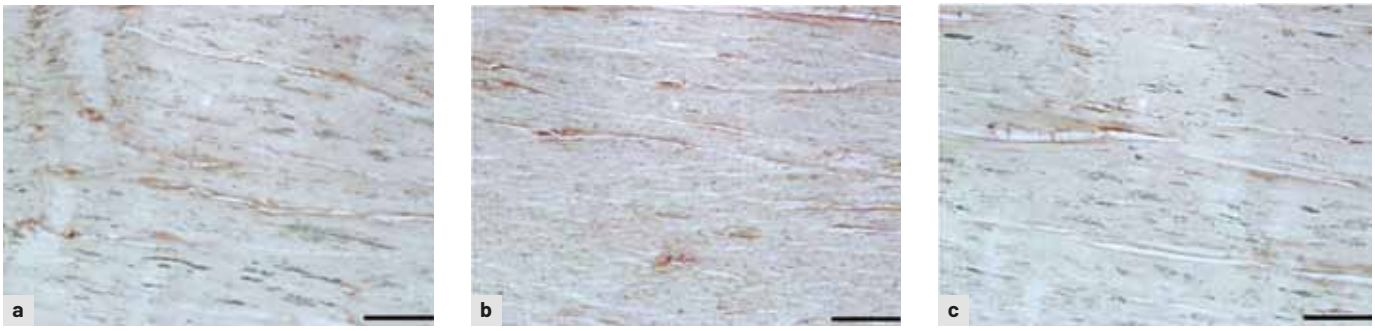


Fig. 2. **Representative photographs showing the H&E staining from rat Achilles tendons in CON (a), MTR (b), and STR (c) groups at eight weeks (n = 6). Fig. 2d shows the cell density in each group**

(Data are shown as mean ± SD; * p < 0.05 compared to the CON group; ** p < 0.05 compared to the MTR group). The scale bar represents 100 μm.



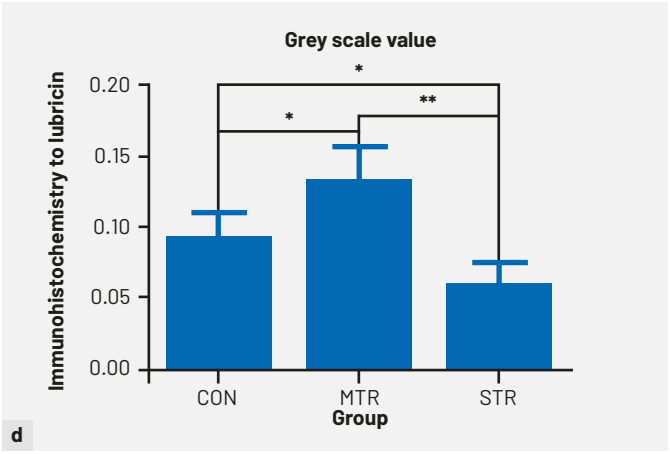


Fig. 3. **Representative photographs showed the immunohistochemical staining for lubricin from rat Achilles tendons in CON (a), MTR (b), and STR (c) groups at eight weeks (n = 6). Fig. 3d shows an immunohistological analysis of lubricin in each group**

(Data are shown as mean ± SD; * p < 0.05 compared to CON group; ** p < 0.05 compared to MTR group). The scale bar represents 50 μm.

CON, MTR, and STR, after eight weeks. Fig. 3 shows the results of the immunohistological analysis of lubricin. Results indicated that at eight weeks, the MTR group exhibited a significantly higher lubricin expression (0.17 ± 0.004) than the CON group (0.14 ± 0.003). However, lubricin expression in the STR group (0.12 ± 0.006) was significantly lower than that in the CON or MTR groups. These observations suggested that MTR intervention may enhance lubricin expression, whereas STR intervention may lead to a decline in lubricin expression.

Western blotting

The study utilized Western blotting was used to detect the expression of the lubricin protein, as shown in Fig. 4a. These results corroborated the observations of immunohistological analysis of lubricin. The data suggest that the MTR group exhibited a noteworthy increase in lubricin protein expression at eight weeks compared to the CON group ($p = 0.035$). Conversely, the STR group showed significantly reduced lubricin protein expression compared to the CON and MTR group ($p = 0.036$ and $p = 0.021$, respectively; Fig. 4b).

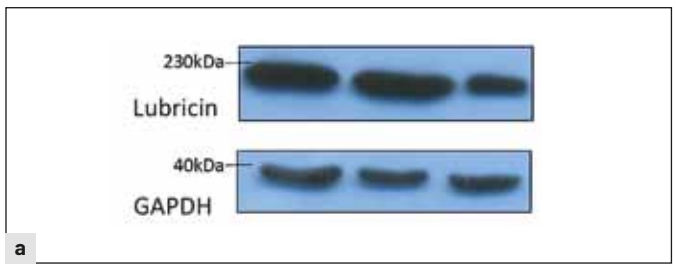
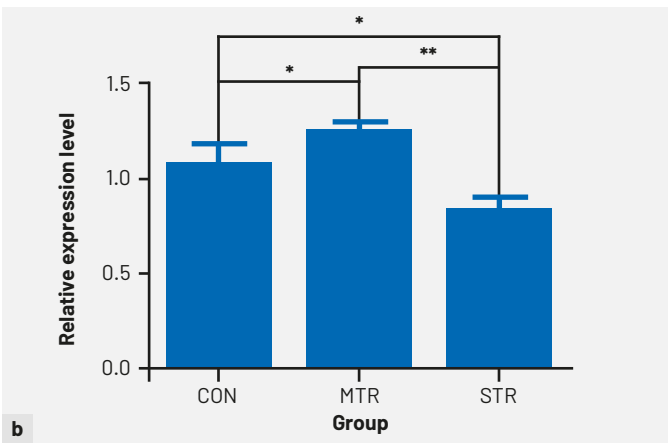


Fig. 4. **Representative western blotting images showing protein expression of lubricin (a). Fig. 4b shows the quantification of lubricin protein expression in rat Achilles tendons in each group (n = 6)**

(Data are expressed as the mean ± standard deviation. * p < 0.05 compared to CON group; ** p < 0.05 compared to MTR group).



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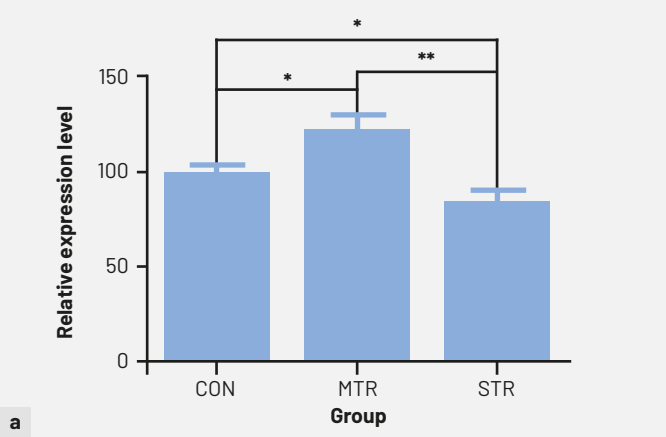

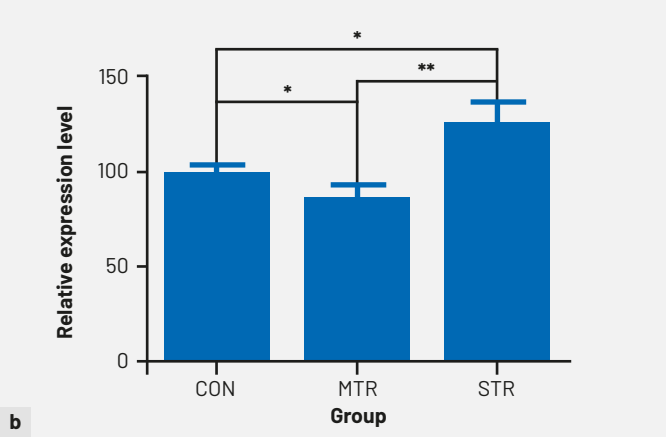

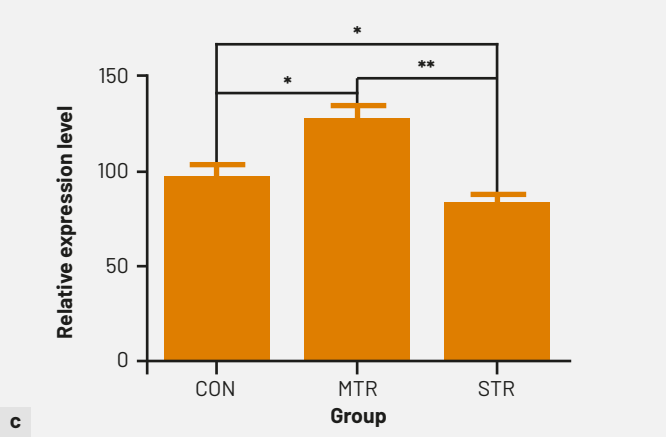

Fig. 5. **The mRNA expression levels of TGF-β1 (a), IL-1 (b), and lubricin (c) in rat Achilles tendons for each group, as determined by RT-PCR (n = 6).**

Data are presented as mean ± SD. *p < 0.05 vs CON; **p < 0.05 vs MTR.

Quantitative real-time polymerase chain reaction (qRT-PCR)

The following study examined the changes in mRNA expression of TGF-β1 (Fig. 5a), IL-1 (Fig. 5b), and lubricin (Fig. 5c) in the Achilles tendon of rats in the CON, MTR, and STR groups for eight weeks. The results indicated that after eight weeks, the expression of TGF-β1 was significantly upregulated in the MTR group compared to that in the CON group ($p = 0.034$). Conversely, it was significantly downregulated in the STR group compared to that in both the CON and MTR groups ($p = 0.042$ and $p = 0.023$, respectively). Additionally, the gene expression of IL-1 was significantly downregulated in the MTR group compared to the CON group ($p = 0.037$), but significantly upregulated in the STR group compared to both the CON and MTR groups ($p = 0.039$ and $p = 0.025$, respectively). Furthermore, the expression of lubricin was significantly upregulated in the MTR group compared to the CON group ($p = 0.020$), whereas it was significantly downregulated in the STR group compared to both the CON and MTR groups ($p = 0.021$ and $p = 0.033$, respectively). These findings suggest that the MTR and STR groups evoke distinct patterns in the mRNA gene expression of TGF-β1, IL-1, and lubricin in the Achilles tendon of rats after eight weeks.

DISCUSSION

The Achilles tendon is the strongest and most strained tendon in the human body (19). It is an essential tendon that connects calf muscles to the heel bone, facilitating walking, running, and jumping. Despite its importance, it is susceptible to injuries that can lead to significant disability and functional limitations. As a result, it is one of the most common tendons injured, posing a significant challenge for orthopedic surgeons (3). During exercise, the Achilles tendon serves two primary functions: to transmit load along the long axis and to stretch when loaded to store energy, which can later be released into the system (18). Therefore, it is recognized as an energy-storing tendon. In vivo, the Achilles tendon can experience strains of over 10%, whereas positional tendons, such as the anterior tibialis tendon, are generally subjected to smaller strains of approximately 2–3% (9, 19). This demanding mechanical environment makes energy-storing tendons more susceptible to injuries known as tendinopathies (18).

During the natural process of stretching and recoiling, the Achilles tendon, fascicles, and bundles of muscle fibers, which are bound together by collagen fibers, glide between adjacent tendon fascicles, and surrounding tissues (21). Collagen fibers are the predominant structural components and major contributors to mechanical force transmission (19). Lubricin plays a crucial role in the function of energy-storing tendons by enabling more elastic and recoverable fascicle sliding that enhances the loading transmission efficiency. Energy-storing tendons rely on lubricin between the fascicles

to facilitate this process. The reduction in lubricin is associated with increased interfascicular friction and energetic cost, which may lead to an increased risk of rupture (6, 7).

This indicates that lubricin plays a pivotal role in ensuring the optimal functioning of tendons, particularly those with energy-storing capabilities. A thorough understanding of the intricate interactions among lubricin, collagen fibers, and fascicles is vital for maintaining the health of these tendons and preventing potential injuries. Therefore, fully comprehending the complex mechanics and implications of these interactions is crucial.

The current study focused on utilizing a running treadmill model featuring various speeds and inclinations to depict different exercise intensities to distinguish between moderate and strenuous exercise. Our findings indicate that collagen fibers in the rat Achilles tendon, after eight weeks, exhibited a crimping and elastic pattern in the CON and MTR groups, whereas they were sub-ruptured in the STR group. Furthermore, we assessed changes in lubricin content in the rat Achilles tendon after eight weeks. The principal outcome revealed that MTR resulted in an increased lubricin content in the Achilles tendon, while STR decreased the lubricin content. Our previous study, employing a similar rat model, demonstrated that running impacts the immunolocalization and gene expression of lubricin in cartilage in an intensity-specific manner (16). This study provides additional evidence that mechanical factors play a significant role in lubricin metabolism in vivo.

In this study, we analyzed the mRNA expression of TGF-β1 and IL-1 to elucidate the mechanisms involved. The findings indicated that TGF-β1 expression was significantly higher in the MTR group than in the CON group, while it was significantly lower in the STR group than in the CON or MTR group. Moreover, TGF-β1 expression is higher after moderate exercise and lower after strenuous exercise (17, 23, 28). Previous studies have shown that TGF-β1 can stimulate tendon fibroblasts and facilitate lubricin synthesis in tendons (8, 11, 30).

Furthermore, histological analysis showed that the cell density in the Achilles tendon sections significantly increased in the MTR group after eight weeks compared to that in the CON or MTR group. Studies have also reported that tenocytes can express lubricin (2, 14, 24). As a result, it can be concluded that moderate exercise triggers an increase in lubricin content in the Achilles tendons by upregulating TGF-β1 expression. This leads to better lubrication, reduced gliding resistance, and improved wear protection, resulting in enhanced efficiency of the loading transmission.

Additionally, the mRNA expression of IL-1 was significantly reduced in the MTR group compared with that in the CON group. Conversely, the STR group demonstrated a marked increase in IL-1 expression, which exceeded that in the CON or MTR groups. Previous research has suggested that repetitive microinjuries caused by intense exercise can lead to the upregulation of IL-1, a typical pro-inflammatory cytokine (4, 26). Additionally, studies have shown that IL-1 can decrease lubricin expression and potentially inhibit cell proliferation. These observations are consistent with the findings of H&E staining, which demonstrated a significant reduction in cell density in the Achilles tendon sections of the STR group, in contrast to both the CON and MTR groups, after eight weeks. Thus, these results suggest that the downregulation of lubricin content, caused by a dramatic increase in IL-1 expression following intense exercise, may enhance interfascicular tribology, leading to tendinopathy or even tendon rupture (1). This study had a few limitations. First, it measured lubricin expression in tendons at a single time point, specifically at eight weeks. Second, the expression of lubricin may differ between rodents and humans, which could affect the relevance of the results to humans. Third, this study only examined changes in lubricin in the extracellular matrix (ECM) without considering other molecules that might also contribute to tendon function. Finally, various factors can affect lubricin expression in tendons, including age, medication usage, tissue fatigue, and infection.

CONCLUSIONS

The present study revealed that the impact of treadmill running on lubricin content in rat Achilles tendons is directly proportional to exercise intensity. Moderate exercise has been observed to enhance lubricin content and improve sliding and recoil properties of the Achilles tendon. In contrast, strenuous exercise may decrease lubricin content and increase the risk of tendinopathy and tendon rupture, as it raises the interfascicular tribology. The study recommends further research on this topic with multiple time points and timeframes to confirm and expand upon these findings. ■

Abbreviations

GAPDH	glyceraldehyde-3-phosphate dehydrogenase
H&E	hematoxylin-eosin
IL-1	interleukin-1
MTR	moderate treadmill running
qRT-PCR	quantitative real-time polymerase chain reaction
STR	strenuous treadmill running
TGF-β1	transforming growth factor-β1

Acknowledgements

We express our gratitude to Mr. Peiran Zhao for technical support and Dr. Vidmi Taolam Martin for proofreading the manuscript in English. We highly valued their contributions.

Availability of data and materials

The datasets produced and examined in this study are available from the corresponding authors upon request.

Ethics approval and consent to participate

All experiments were performed in accordance with the guidelines for animal care and use approved by the animal ethics committee of Nanfang Hospital, Southern Medical University.

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