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Graded Compression Sleeves Could Promote Healing or Fibrosis in Mechanically Loaded Tendons by Upregulating the Expression of miRNA 21-5p

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Abstract: MiRNA 21-5p (miR-21-5p) plays a critical role in tendon healing by regulating fibroblast production and migration. However, its excessive upregulation during early healing stages may lead to pathological fibrosis. While graded compression sleeves are widely used as preventive and therapeutic aids for tendon injuries, their effects on circulating miRNAs remain largely unexplored. This exploratory case study investigated how compression sleeves affect the acute expression of miR-21-5p in mechanically loaded tendons of the upper extremities. Two healthy males aged 20 and 24 years with no known tendon injuries were recruited - one sedentary individual and one competitive volleyball player, representing different levels of habitual tendon loading. During their initial visit, anthropometric measurements and maximal grip strength (MGS) of the dominant hand were assessed. Participants then completed a standardized hand-gripping protocol (2-second grip, 3-second rest for 2 minutes at 60% MGS) under two conditions: with and without graded compression sleeves on both upper limbs. Venous blood samples were collected before and after completing each task to evaluate circulating miR-21-5p expression. Total circulating miRNAs were extracted and reverse transcribed, with miR-21-5p expression levels analyzed relative to the small nuclear RNA (siRNA) U6 using the $2^{-\Delta\Delta Ct}$ method. Results revealed distinct participant-specific responses: compression sleeves circulating miR-21-5p expression in the sedentary participant but increased expression in the volleyball player. This differential response suggests compression sleeves may modulate miRNA expression patterns based on prior tendon loading history. These preliminary findings indicate that graded compression sleeves might differentially influence healing and fibrosis processes in mechanically loaded tendons, particularly in individuals with a history of repetitive upper limb use. The observed upregulation in the volleyball player may reflect a protective adaptive response to chronic loading. Future research will incorporate larger sample sizes and analyze expressions of extracellular matrix (ECM)

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molecules (IL-6, TNFα, and matrix metalloproteases 9 and 13) to better elucidate miR-21-5p's role in tendon healing and fibrosis when graded compression sleeves are used.

Keywords: miR-21-5p, compression sleeves, tendon mechanical load, fibrosis.

1. Introduction

Mechanical tendo load is a significant factor contributing to the development or worsening of work-related musculoskeletal disorders (WMSDs), especially in occupations involving repetitive or forceful tasks. Sustained or excessive loading of the tendons can lead to microtears and inflammation. If these injuries are not allowed to heal, they can progress to chronic tendinopathies (Cook & Purdam, 2009). WMSDs impose a significant economic burden, costing billions of dollars annually in health care costs and productivity losses. In the United States, employers spend over $20 billion every year on direct costs associated with WMSDs, with indirect costs estimated to double that amount (OSHA, 2024) These conditions are the leading cause of days away from work, particularly among labor-intensive occupations, including manufacturing, construction, and health care (BLS, 2024). To reduce the risks, interventions such as the use of compression sleeves have been explored. Compression garments may enhance proprioception, reduce muscle oscillation, and potentially support tendon health by modulating local circulation and inflammation (Ali et al., 2007). Even though more research is needed, these ergonomic interventions may reduce the incidence and severity of MSDs in high-risk environments.

MicroRNAs (miRNAs) are small, non-coding RNA molecules of 18-24 nucleotides that regulate post-transcriptional gene expression. miRNAs bind to target messenger RNA (mRNA), leading to degradation or translational repression (Bartel, 2004). In tendon biology, miRNAs are important mediators of mechanotransduction, the process of converting mechanical stimuli into cellular responses (Nakamichi & Asahara, 2024). Mechanical tendon loading influences miRNA expression, which can alter key cellular functions, including inflammation, extracellular matrix (ECM) turnover, and cell proliferation (Dubin et al., 2018). The changes in the expression of these miRNAs in response to tendon mechanical loading suggest their potential as biomarkers and therapeutic targets in tendon injury and repair.

One of the main miRNAs involved in tendon health is miR-21-5p, a miRNA associated with fibrosis and inflammation in musculoskeletal tissues. Mir-21-5p is known to be upregulated in response to mechanical stress and strain, and the increase is linked to downstream signaling pathways promoting the activation of fibroblasts in the ECM, two key processes in tendon remodeling and pathology (Li et al., 2010). In tenocytes, mechanical loading can lead to an increase in mir-21-5p expression, suppressing the regulators of the central fibrosis mediator pathway TGF-β/SMAD7-SMAD2/3(Song et al., 2024). This pro-fibrotic shift may contribute to the development of tendinopathies in chronic or excessive loading conditions. On the contrary, modulation of mir-21-5p in mechanical unloading or therapeutic inhibition has been shown to reduce markers of fibrosis and to improve tenocyte homeostasis (Cui et al., 2019; Lyu et al., 2023).

Based on the association between mechanical tendon load and tendon pathology and the role of miR-21-5p in fibrosis and tendon inflammation, a better understanding of strategies modulating these molecular pathways may help prevent or treat tendinopathies. One of these strategies is using graded compression sleeves that may influence local mechanical and physiological responses. Therefore, the aim of this study was to investigate the effects of wearing graded compression sleeves on the expression of circulating miR-21-5p after completing a tendon loading task.

2. Methods

2.1 Participants

Two apparently healthy, 20-year-old and 24-year-old males from the University of Texas at El Paso agreed to participate in the study. Only male participants were included to minimize the possible effects of estradiol and progesterone on miRNA expression (Schisterman et al., 2014). Both participants had no history of tendon injuries - one sedentary individual and one competitive volleyball player—representing different levels of habitual upper extremity tendon loading. Participants were asked to continue their normal routine if they engaged in regular physical activity.

2.2 Anthropometric Measurements

Body weight (kg) and height (m) were measured using a Detecto™ scale with a stadiometer. Body mass index (BMI) was calculated by dividing the weight in kilograms by the square of the height in meters (BMI = weight (kg) / height (m^2). Resting blood pressure (mmHg) and heart rate (BPM) were measured using an Omron™ digital blood pressure monitor after the participants rested for at least 10 minutes after arriving at the laboratory.

2.3 Surface Electromyography and Maximal Grip Strength

During each visit, before the start of the hand-gripping task, the research assistant attached dual surface electromyography (sEMG) electrodes in the extensor digitorum longus and the flexor digitorum superficialis muscles of the participant's dominant hand. After the electrodes were attached, the participants were asked to hold a wireless hand dynamometer with their dominant hand, grip it as hard as possible, and maintain a 90° angle at the elbow (Figure 1a, 1b, and 1c). The maximum force (N) was recorded during the grip strength assessment and used to calculate 60% of the participant's maximal grip force for the hand-gripping task.

Figure 1. Participant showing having a sEMG electrode placed on the extensor digitorum muscle (a). Participant showing a sEMG electrode placed on the flexor digitorum superficialis muscle (b). Participant showing gripping the hand dynamometer while maintaining a 90° angle at the elbow (c).

2.4 Blood Sampling and Lactate Measurements

After measuring the maximal grip strength, a registered nurse (RN) used a Vacutainer Safety-Lok Blood Collection Set to procure a sample from the mid-cubital vein of the dominant and non-dominant arms. The needle was secured using Tegaderm to prevent it from moving during procedure (Figure 2). A blood sample of approximately 20 cc was obtained from the dominant arm (localized) and the non-dominant arm (systemic) before and after the hand-gripping task. Once the 20-cc sample was obtained, a small drop was used to measure circulating blood lactate using the Nova Biomedical lactate meter. The remaining sample was immediately centrifuged to separate the plasma from red and white blood cells. A small plasma sample of about 100 µL was used for miRNA extraction, and the rest was stored at -80°C.

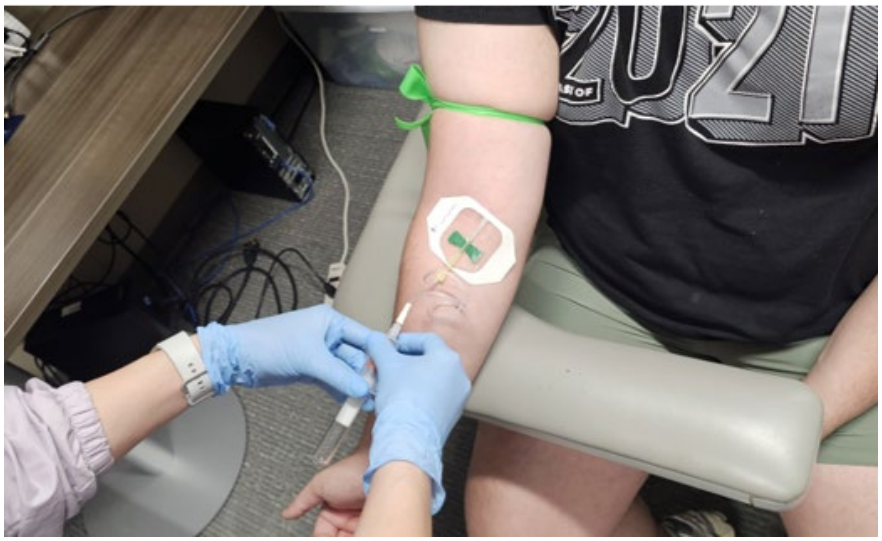

Figure 2. A Vacutainer Safety-Lok Blood Collection Set was inserted into the mid-cubital veins of both arms to procure a blood sample before and after the hand-gripping task.

2.5 Hand Gripping Task

The participants were asked to grip the hand dynamometer to produce and maintain a force equal to 60% of the maximal grip for two seconds and rest for three seconds. The participants followed this pace using a metronome. The cycle was repeated for two minutes. The participants completed the same task under two randomly assigned conditions: without sleeves (NS) and with sleeves (S) (Figure 3a, Figure 3b).

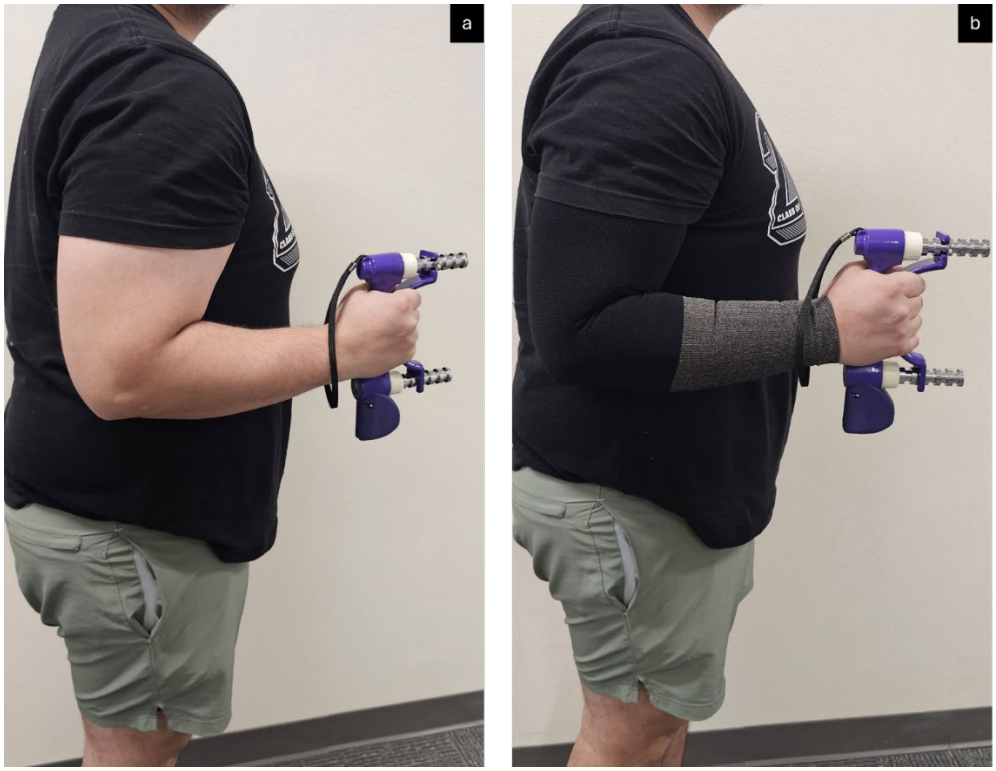

Figure 3. Participant showing the different hand-gripping task conditions. a) no sleeves. b) sleeves

2.5 miR-21-5p Expression

Total circulating miRNA was extracted using the Qiagen miRNeasy kit, following the manufacturer's instructions, and stored at -80°C until all samples were extracted and ready for analysis. Once all the miRNA was extracted from the samples, it was reverse transcribed into complimentary DNA (cDNA) using the Taqman Advanced miRNA cDNA synthesis kit. The target miR21-5p was amplified using the Taqman Fast Advanced Master Mix, and their expression was assessed using the StepOne PCR system. The relative expression of miRNA was determined using the $2^{-\Delta\Delta Ct}$ method, with small nuclear RNA U6 (snU6) serving as the internal loading control for normalization. All results are presented as fold changes relative to snU6.

3. Results

The analysis of circulating miR-21-5p is presented as the relative change before and after the hand gripping task. The healthy sedentary subject (subject 1) showed an overall low expression in both arms, with a consistently higher expression in the right (dominant arm), and no marked difference between wearing and not wearing compression sleeves. The healthy active subject (volleyball player; subject 2) showed a greater expression in the right arm compared to subject 1, and wearing sleeves greatly increased the expression versus not wearing sleeves (Figure 4.).

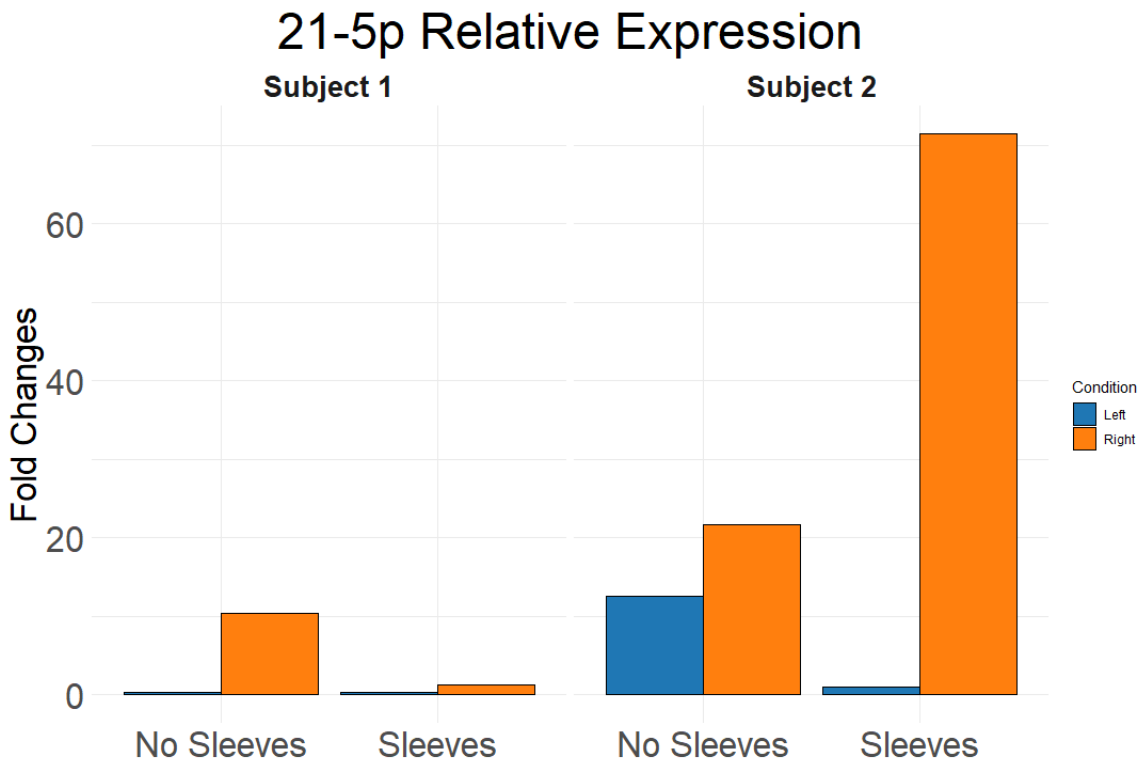

Figure 4. Relative expression of miR-21-5p shows a greater expression in subject 1. Furthermore, there is a greater expression with the use of compression sleeves in subject 2.

4. Concluding Remarks and Future Directions

3. Citations and References

The different expression of miR-21-5p between subjects shows the potential of this miRNA as a mechanosensitive regulator influenced by different conditions, including compression and tissue health. Subject 2 showed an elevated expression with and without using graded compression sleeves, with the highest expression using sleeves. mir-21-5p has been shown to have a dual function in tissue remodeling, supporting regeneration by promoting fibroblast activation and survival, and

activating the pro-fibrotic signaling pathways such as TGF-β/Smad (Cui et al., 2019). These elevated levels in an overused tissue with the addition of compression sleeves may reflect an imbalanced environment, which could shift towards the development of fibrosis or be beneficial for ECM remodeling (Wu et al., 2022).

The marked differences across subjects, dominant limbs, compression, and possible tissue health show that circulating levels of miR-21-5p do not depend on a single factor. A more detailed study of other molecules involved in tendon fibrosis or ECM remodeling is necessary to have a better understanding of the effects of graded compression on mir-21-5p expression (Cui et al., 2019; Zhu et al., 2019).

In conclusion, this preliminary data suggests that compression sleeves can elevate the expression of miR-21-5p, particularly in patients with constant overuse of the upper limbs. A more comprehensive study of other key molecules involved in fibrosis and EMC remodeling is needed to determine the role of this increase in miR-21-5p. Future research will assess the changes in the matrix metalloproteases associated with collagen turnover and TGF-β1.

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