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Using Graded Compression Sleeves Increases the Expression of MIR 29a-3p in Mechanically Loaded Tendons

Valeria Fontes[1], Daniel Conde[2], Josdell M. Guerra Ruiz[1], Carlos Saenz[3], Raul Zubia[3], Manuel Gomez[4], Ricardo Rangel[5], Jacen M. Moore[6], and Gabriel Ibarra-Mejia[1]

[1]Department of Public Health Sciences, The University of Texas at El Paso

[2]Physical Therapy and Movement Sciences Department, The University of Texas at El Paso

[3]Department of Kinesiology, The University of Texas at El Paso

[4]Interdisciplinary Health Sciences Ph.D. Program, The University of Texas at El Paso

[5]Bio Eternal Science Lab, Mexico City, Mexico

[6]Department of Diagnostic and Health Sciences, The University of Tennessee Health Science Center

Corresponding author's Email: vfontes@miners.utep.edu

Author Note: Valeria Fontes has an MD degree from Universidad Autonoma de Guadalajara and is currently a Master's in Public Health student at the University of Texas at El Paso. Dr. Daniel Conde has a Ph.D. in Interdisciplinary Health Sciences from the University of Texas at El Paso. He is currently a postdoctoral researcher in the Physical Therapy and Movement Sciences Department at the University of Texas at El Paso. Josdell M. Guerra Ruiz has a B.S. in Biological Sciences and is currently a Master's in Public Health student at the University of Texas at El Paso. Carlos Saenz is an undergraduate student in the Kinesiology Department and a Research Assistant in the Bioergonomics Lab at the University of Texas at El Paso. Mr. Zubia has a Bachelor's and Master's in Kinesiology and a Bachelor's in Nursing from the University of Texas at El Paso. He is a full-time lecturer at the University of Texas at El Paso Kinesiology Department and a Licensed Registered Cardiology Nurse at El Paso Cardiology Associates. Manuel Gomez has a Master's in Kinesiology from the University of Texas at El Paso. He is a Ph.D. student and Graduate Research Associate at The University of Texas at El Paso. Dr. Ricardo Rangel-Martinez holds a Ph.D. degree in Biological Sciences. He is the scientific director of the Bio Eternal Science Lab in Mexico City, Mexico. Dr. Jacen Moore holds a Ph.D. in Experimental Pathology. He is an Associate Professor in the Department of Diagnostic and Health Sciences at the University of Tennessee Health Science Center. Dr. Gabriel Ibarra-Mejia has an MD and MS degree from Universidad Autonoma de Ciudad Juarez, an MS degree in Ergonomics from Lulea Tekniska Universitet in Sweden, and a Ph.D. in Environmental Science and Engineering from the University of Texas at El Paso. He is currently an Assistant Professor in the Department of Public Health Sciences at the University of Texas at El Paso.

Abstract: MiRNA 29a-3p (miR-29-3p) plays a significant role in tendon tissue remodeling following injury by selectively regulating collagen expression. While its upregulation reduces collagen type III (COL3) expression without affecting type I collagen, downregulation of miR-29a-3p may be beneficial during early tendon healing stages when a COL3 framework is essential for proper tendon repair. Although graded compression sleeves are widely used in both the prevention and treatment of tendon injuries, their effects on circulating miRNAs remain inadequately understood. This exploratory study investigated how compression sleeves affect the acute expression of miR-29a-3p in mechanically loaded tendons of the upper extremities. Two healthy males (aged 20 and 24 years) with no history of tendon injuries were recruited - one sedentary individual and one competitive volleyball player—representing different levels of habitual upper extremity tendon loading. Following baseline anthropometric measurements and assessment of maximal grip strength (MGS) of the dominant hand, participants 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 each task to evaluate circulating miR-29a-3p expression. Total circulating miRNAs were extracted and reverse transcribed, with expression levels analyzed relative to small nuclear RNA (snRNA) U6 using the $2^{-\Delta\Delta Ct}$ method. Results revealed comparable baseline expression of miR-29a-3p between participants. Notably, compression sleeves increased circulating miR-29a-3p expression in the dominant hand of the volleyball player, and decreased expression in the non-dominant hand of the same participant. These findings suggest that graded compression sleeves may support early-stage tendon healing processes by increasing miR-29a-3p expression, potentially suppressing excess collagen formation providing

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anti-fibrotic protection to the tissue. Future research will examine miR-29a-3p expression at various stages of tendon healing to determine how its modulation by compression therapy correlates with tissue quality and functional outcomes, potentially informing more targeted therapeutic interventions for tendon rehabilitation.

Keywords: miR-29a-3p, compression sleeves, tendon mechanical load.

1. Introduction

Mechanical tendon 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, 2023).These conditions are the leading cause of days away from work, particularly among labor-intensive occupations, including manufacturing, construction, and health care (BLS, 2022). 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 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.

MicroRNAs modulation in collagen synthesis, extracellular matrix remodeling and localized tendon mechanical load are an understudied field. In this study, we addressed this gap by exploring miR29a-3p as a potential biomarker and therapeutic target in tendon healing and remodeling. This, by exploring molecular expression of specific MicroRNA in early tissue repair.

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. Participant 2 plays volleyball, which is considered an activity with repetitive use of the upper limbs. 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° at the elbow (Figure 1a, 1b, and 1c). The maximal amount of 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. a) Participant showing having a sEMG electrode placed on the extensor digitorum muscle. b) Participant showing a sEMG electrode placed on the flexor digitorum superficialis muscle. c) Participant showing gripping the hand dynamometer while maintaining a 90° at the elbow.

2.4 Blood Sampling, miRNA Extraction and Lactate

After measuring the maximal grip strength, a registered nurse (RN) inserted an intravenous catheter with an extension line into the mid-cubital vein of the dominant and non-dominant arm. The catheter was secured using Tegaderm to prevent it from moving during the hand-gripping task (Figure 2a). A blood sample of approximately 20 cc was obtained from the dominant hand (localized) and the non-dominant hand (systemic) before and after the hand-gripping task. To ensure a reliable sample was obtained, the RN washed the line with a saline solution of approximately 10 cc before obtaining a small "waste" sample; once the sample was discarded, a 20-cc sample was obtained and immediately centrifuged to separate the plasma from red and white blood cells. Total miRNAs were immediately extracted and stored at -80°. The remaining plasma samples were also stored at -80°C.

Circulating blood lactate was measured using the Nova Biomedical lactate meter from a drop of blood of approximately 100 µL obtained from the 20-cc sample. A pipette was used to obtain and load the sample into the lactate meter strip.

2.5 Blood Flow Restriction and Graded Compression Sleeves

The correct sleeve size was determined by measuring the wrist circumference following the manufacturer's instructions. The compression sleeves created a graded compression in the forearm equal to 12 mmHg at the wrist and 8 mmHg just below the elbow (Figure 3).

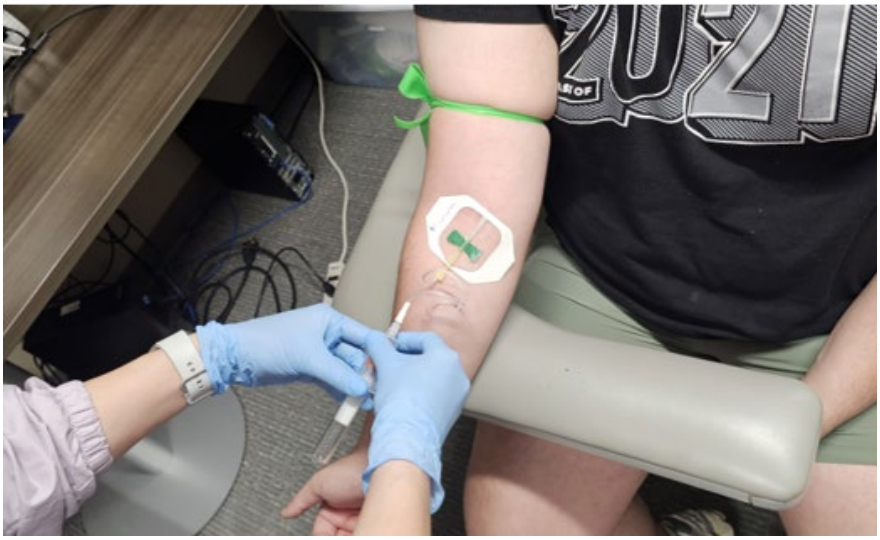

Figure 2. Venous blood samples. a) An intravenous catheter attached to an extension line was inserted into the mid-cubital vein of the arm to procure a blood sample before and after the hand-gripping task.

Figure 3. The participant is seen wearing the graded compression sleeve. The gray part of the sleeve creates a graded compression equal to 12 mmHg distal to 8 mmHg proximal.

2.6 Hand Gripping Task

The participant was asked to grip the hand dynamometer, producing and maintaining a force equal to 60% of the maximal grip for two seconds and resting for three seconds. The participants repeated this cycle until they completed two minutes. The participants completed the same task under two conditions randomly assigned (Figure 4a, Figure 4b).

1. With no sleeves (NS)
2. With sleeves (S)

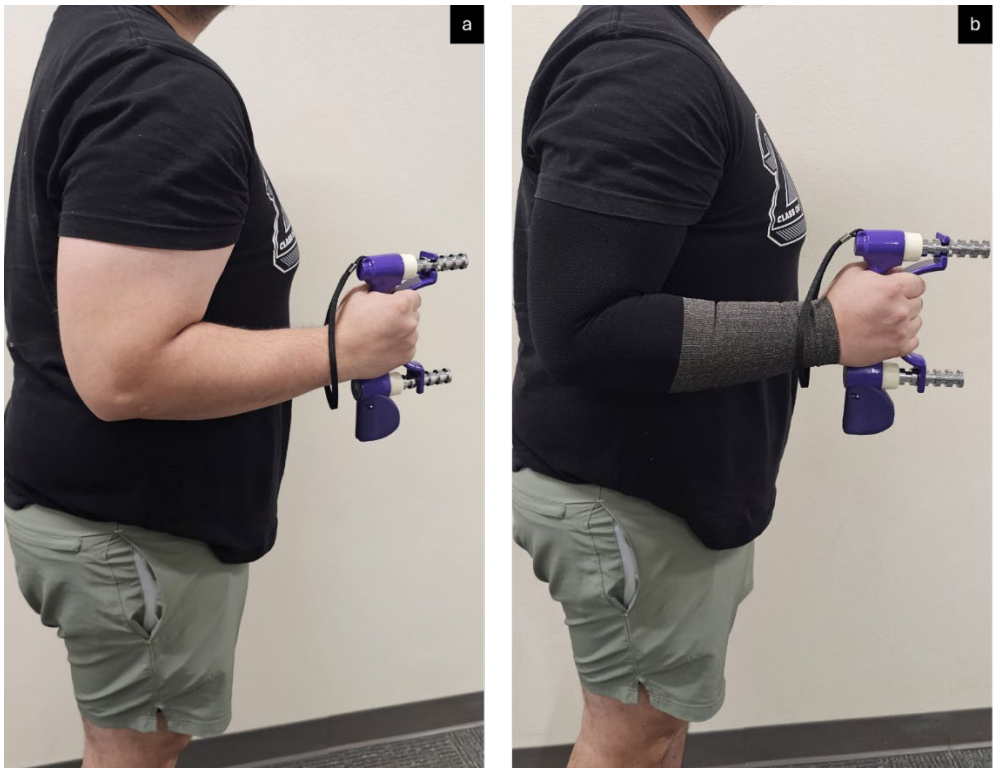

Figure 4. Participant showing the different hand-gripping task conditions. a) no sleeves. b) sleeves

2.7 miRNA 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 miRNA 29a-3p 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 study revealed minimal expression of miR29a-3p under all conditions for the sedentary participant (subject 1). The relative fold changes presented on figure 5 show a slight increase of 29a-3p in both limbs when compression was applied. In contrast, compression sleeves increased circulating miR-29a-3p expression in dominant hand of the volleyball player (subject 2) while decreasing it in the non-dominant (left) hand. These findings suggest that graded compression

sleeves may support early-stage tendon healing and remodeling processes by increasing localized miR-29a-3p expression while decreasing systemic expression. This potentially controlling excess collagen gene expression as a potential protective anti-fibrotic response. (Figure 5).

Future research will examine miR-29a-3p expression at various stages of tendon healing to determine how its modulation by compression therapy correlates with tissue quality and functional outcomes, potentially informing more targeted therapeutic interventions for tendon injury prevention and rehabilitation.

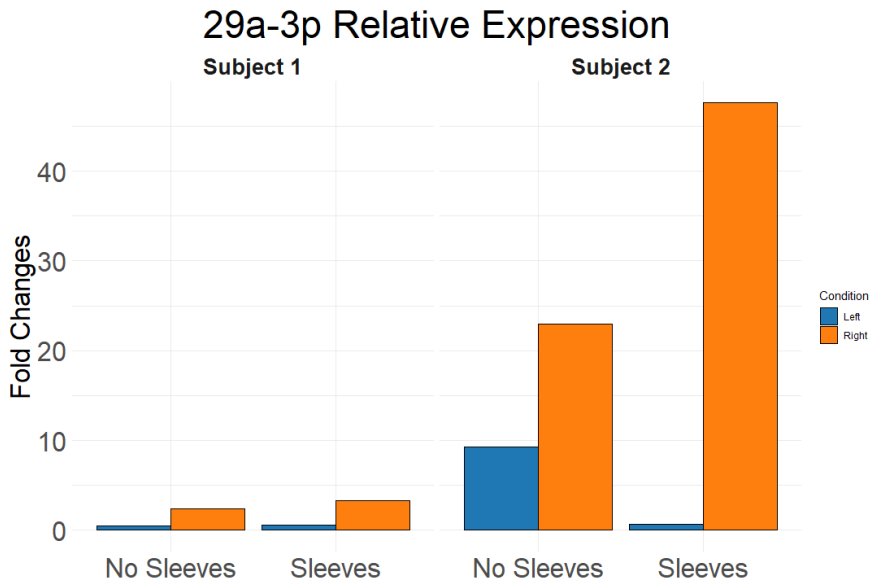

Figure 5. Fold changes of miR29-3p expression compared to snU6 in left and right upper limb of participant 1 and participant 2.

4. Discussion

The results of this experiment suggest a localized response in the expression of miR-29a-3p after mechanically loading the tendons of the forearm. This response seems to be associated with the use of graded compression sleeves and the mechanical loading of the tendons. This response is shown by the increase in miR29a-3p in the dominant arm with sleeves of both participants and a notably decrease in the non-dominant hand of subject 2.

Although three of the results do not fully align with findings in the literature—where post-injury downregulation is typically reported, as observed in the left arm of Subject 2, it is important to note that the application of compression suggests an upregulation of the miRNA. Importantly, this response may reflect localized rather than systemic effects. The discrepancy from previously published work may relate to one of this study's limitations, namely the small sample size. Nevertheless, these preliminary data will guide refinements to our methods for evaluating miRNAs associated with tendon response, including their potential use as biomarkers of tendon mechanical load, and will contribute to foundational knowledge for future therapeutic applications. Additionally, the results will help us assess the specific effects of adding compression to mechanically loaded tendons.

Future studies by our research group will aim to deepen our understanding of how mechanical load shapes the tendon microenvironment and to further clarify the role of miRNAs in tendon health, recovery, and injury. We plan to investigate additional miRNAs implicated in tendon damage and repair, such as miR-210-3p and miR-145-5p, and to increase our sample size, potentially focusing on specific populations such as manual laborers. This expanded knowledge will be essential for developing more effective work-to-rest ratios and may also offer valuable insights into the therapeutic potential of miRNAs in the treatment of work-related musculoskeletal disorders (WMSDs).

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