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The following email was sent to Francisco Camolesi Ide from Medicina (Ribeirão Preto) regarding Impact of Cortical Representation of Lumbar Stabilizing Muscles in Chronic Low Back Pain Conditions: A Systematic Review.

You are receiving a copy of this notification because you are identified as an author of the submission. Any instructions in the message below are intended for the submitting author, Francisco Camolesi Ide, and no action is required of you at this time.

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Acute effect of scapular mobilization with associated myofascial release on butterfly performance: Randomized clinical trial

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ABSTRACT

Introduction: To evaluate the acute effect of scapular mobilization with associated myofascial release compared to scapular mobilization without myofascial release on butterfly stroke sports performance. Design: Randomized clinical trial.

Method: Pilot study that non-probabilistically convenience sampling that selected butterfly swimmers who were simply randomized into three groups to receive the standard protocol (scapular mobilization with release of the subscapularis muscle by the lateral edge of the scapula and rib cage detachment) in intervention group (IG), sham group (SG) (scapular mobilization without subscapularis muscle release and without rib cage detachment) or no intervention in control group (CG). We evaluated the stroke frequency, length, and average speed of 30 swimmers using the 8.15 Kinovea® motion analysis system.

Results: The findings showed that, compared to the CG and IG, the SG showed a significant reduction in mean velocity ($p = 0.002$; $p = 0.02$, respectively), stroke frequency ($p = 0.002$; $p = 0.003$, respectively), and stroke length ($p = 0.01$; $p = 0.05$, respectively).

Discussion: The results showed that manual therapy through scapular mobilization without associated myofascial release with detachment of the scapula from the rib cage worsened the swimming efficiency indicators even after 30 min of application of the technique. The limitations of the studies are related to the sample size, the risk of non-probabilistic contraction bias and the lack of blinding of the evaluators. Thus, the results of this study should be evaluated with caution.

1. Introduction

The butterfly stroke relies on simultaneous action of the upper and lower limbs and discontinuous action of the propulsive forces of the arms and legs (Barbosa, 2004). The propulsive strength of the hands and muscle power are predisposing factors for optimized performance (Hopkins and Hewson, 2001). In competitive swimming, variables, such as mean velocity, frequency, and stroke length, are considered indicators of the efficiency of sports performance (Hay, 1981) and should be part of the athlete's strategic planning (Hannula and Thornton, 2001).

Previous studies (Keskinen et al., 1989; Keskinen and Komi, 1993) have reported a correlation between stroke length and frequency and swimming velocity; that is, an increase in the stroke frequency implies a decrease in the stroke length. According to Alberty et al. (2009) depending on how the frequency and stroke length are coordinated, the average swimming speed is influenced by propulsive and resistive impulses generated by the strokes. The combination of these indicators makes swimming rhythmic and efficient, and the impact of biomechanical changes on stroke performance is apparent (Hannula and Thornton, 2001).

Thus, efficiency indicators rely on biomechanics to evaluate the performance. Farah et al. (2010) showed that biomechanical changes in the shoulder girdle of swimmers, such as decreased mobility and tissue adherence, negatively influence the efficiency of swimming due to changes in muscle recruitment, asymmetry of strength during stroke, and changes in the athlete's trajectory (Aguiar et al., 2010; Vanderlei et al., 2014). The results of the study by Carvalho et al. (2023) show that swimmers who received deep arm massage had no effect on functional performance. The technique and maneuvers (Smith, 2007) of manual therapy aimed at scapular movement with release of the subscapularis muscle by the lateral border of the scapula could restore the

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biomechanical pattern by releasing tissue adhesions from the rib cage (DiGiovanna et al., 1997; O'Sullivan and Schmitx, 2010; Sung et al., 2005), thus allowing sporting movements with lower mechanical cost and consequently better swimming performance (Barbosa et al., 2009; Blanch, 2004).

Exercise therapy has positive effects improving shoulder musculoskeletal risk factors in competitive swimmers (Yoma et al., 2022). In this sense, Barbosa et al. (2009) believes that maneuvers aimed at detaching the scapula from the rib cage can enhance.

However, to date, no study has reported the acute effect of using scapular monitoring techniques with myofascial release compared to scapular release without myofascial release on butterfly swimming performance, as the latter is widely used in clinical practice in moments before sports competitions. Our hypothesis is that a manual therapy technique associated with myofascial release will improve shoulder mechanics and improve swimming indicators. Therefore, the aim of this study was to evaluate the acute effect of scapular mobilization with associated myofascial release compared to scapular mobilization without myofascial release on butterfly stroke sports performance.

2. Methods

2.1. Study design

Randomized clinical trial.

2.2. Study settings

Pilot study that non-probabilistically convenience sampling that selected butterfly swimmers who were simply randomized into three groups to receive the standard protocol (scapular mobilization with release of the subscapularis muscle by the lateral edge of the scapula and rib cage detachment), sham (scapular mobilization without subscapularis muscle release and without rib cage detachment) or no intervention.

2.3. Ethical considerations

This project was approved by the Human Research Ethics Committee of the State University of Santa Catarina (Udesc) (CAAE: 38770514.6.0000.0118; number 972.342). Recruited participants were informed about the research objectives and data collection procedure. After accepting to participate, the individual read and signed the Informed Consent Form, where the rights of the participants were protected.

2.4. Subjects

The participants in this study were selected in an intentional non-probabilistically convenience sampling manner and randomly distributed to one of the three groups (n = 10 per group) using a simple randomization method. The sample was composed of 30 federated man swimmers practicing the butterfly stroke. Participants were collected in the pool at the University of Santa Catarina (Udesc) in the first half of 2016. Inclusion criteria were individuals who were registered with the Brazilian Confederation of Water Sports, residents of Greater Florianópolis, aged between 13 and 25 years, and who had engaged in at least two years of sports practice with a minimum of four weekly workouts. And, as an exclusion criterion, participants who underwent a surgical procedure in the last three months, participants with limb amputation and associated cardiorespiratory disease were considered.

2.5. Evalution of outcome measures

The intervention group (IG) received scapular mobilization with the release of the subscapular muscle by the lateral edge of the scapula and detachment from the rib cage, while the sham group (SG) received scapular mobilization without the release of the subscapularis muscle and without detachment from the rib cage. The control group (CG) did not receive any intervention.

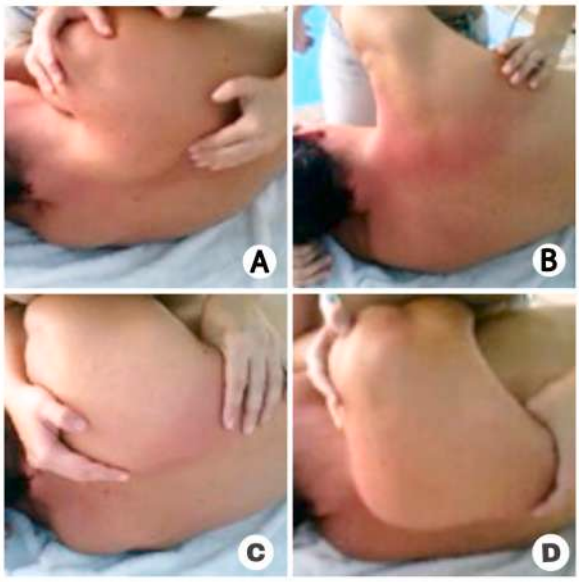

Fig. 1. Intervention technique with scapular mobilization associated myofascial release. Then A) Deep slip in the scapula region. B) Traction of the scapulohumeral joint in the shoulder plane. C) Release of the subscapular region. D) Detachment of the scapula from the rib cage.
Source: The authors, 2016.

Prior to data collection, the swimmers signed an evaluation form and warmed up for 10 min with freestyle swimming. A camera of the model Casio® Exilim EX-FH20 9.1 MP Digital was positioned on the opposite side of the pool to record swim performance, from which the stroke frequency and length as well as the average velocity were calculated. Beginning 5 m in the pool, colored markers were positioned at 10 m intervals on the pool surface for better viewing during the video analysis. All evaluations were performed by a single, blinded evaluator.

2.6. Intervention

2.6.1. Intervention group (IG)

Prior to the intervention, the swimmer was asked to perform the butterfly stroke for 25 m at a maximum speed with an underwater exit. Subsequently, the individual lay in the lateral decubitus position with knees flexed and the homolateral upper limb in a relaxed position. The intervention technique (Fig. 1) of scapular mobilization was performed as follows: A) myofascial release of the superficial tissues (Bronfort et al., 2008; Busquet, 2001; Maitland and Corrigann, 2000; McClure et al., 2006; Moseley et al., 1992; Pickar and Kang, 2006) by deep sliding in the periscapular region; B) glenohumeral traction in the scapular plane; C) release of the subscapular region by the lateral edge of the scapula; and D) detachment and scapular mobilization. Scapular mobilization was performed on both scapulae because it has been reported that unilateral dysfunction causes changes in bilateral activity (Smith, 2007).

Immediately after mobilization, which lasted an average of 10 min, the swimmer was asked to perform the butterfly stroke for 25 m at a maximum speed with an underwater exit. The swimmer then rested in a chair for 30 min. At the end of 30 min, the swimmer was asked to once again perform the butterfly stroke for 25 m at a maximum speed with an underwater exit.

2.6.2. Sham group (SG)

The swimmer was asked to perform 25 m of butterfly stroke at a

Fig. 2. Scapular mobilization without myofascial release.
Source: The authors, 2023.

maximum speed with an underwater exit before mobilization. Subsequently, the individual lay in lateral decubitus, with knees flexed, and the homolateral upper limb in the most relaxed position possible. Only scapular mobilization in the upper inferior, lateral medial, and circular directions was performed. In this mobilization, there was no myofascial release of superficial tissues, glenohumeral traction in the scapular plane, detachment of the scapula from the rib cage, or release of the subscapular region.

At the end of the mobilization, which lasted an average of 10 min, the swimmer was asked to perform the butterfly stroke for 25 m at a maximum speed with an underwater exit immediately after mobilization, rest in a chair for 30 min, and then once again swim the butterfly stroke for 25 m at a maximum speed with an underwater exit, which is represented in Fig. 2.

2.6.3. Control group (CG)

First, the swimmer was asked to perform the butterfly stroke for 25 m at maximum speed with an underwater exit. Then, the individual sat for 10 min (time of scapular mobilization) with clothing to maintain body temperature. At the end of the 10 min seated, the swimmer was asked to perform the butterfly stroke for 25 m at a maximum speed with an underwater exit and then immediately remain seated for another 30 min in a chair. Finally, at the end of 30 min, the swimmer was asked to perform the butterfly stroke for 25 m at a maximum speed with an underwater exit. Finally, for a better visualization of the data collection procedure, a flowchart was created, which is represented in Fig. 3.

A database was organized into spreadsheets for each of the variables, and the data were exported to Microsoft Excel for the preparation of tables and graphs. The primary outcome variable was mean velocity and was evaluated during the initial 10 m of swimming. The average speed was calculated as the distance that the swimmer traveled every second, expressed as meters/second (m/s) (Hay, 1981).

The secondary variables were stroke frequency and length, which were also evaluated during the initial 10 m from launch. The one stroke cycle was counted as the entry of hands through the water surface until the moment the hands next contacted the water surface. The number of strokes was calculated as the number of times the hands came into contact with the water surface. The frequency of strokes was expressed as the number of cycles per time (Hay, 1981). The length of the stroke is the distance traveled by the swimmer and the number of strokes performed in this interval and is expressed as the number of strokes (Hay, 1981).

The Kinovea 8.15® program was used to analyze these variables; this program allows frame-by-frame observation and the ability to advance and rewind images, allowing temporal control of each of the athlete's movements.

2.7. Statistical analysis

Data were tabulated in the Office Excel program and analyzed in the statistical software R version 4.2.1. The sample characterization data were analyzed using descriptive statistics (mean, standard deviation, absolute and relative frequency). Data normality was verified using the

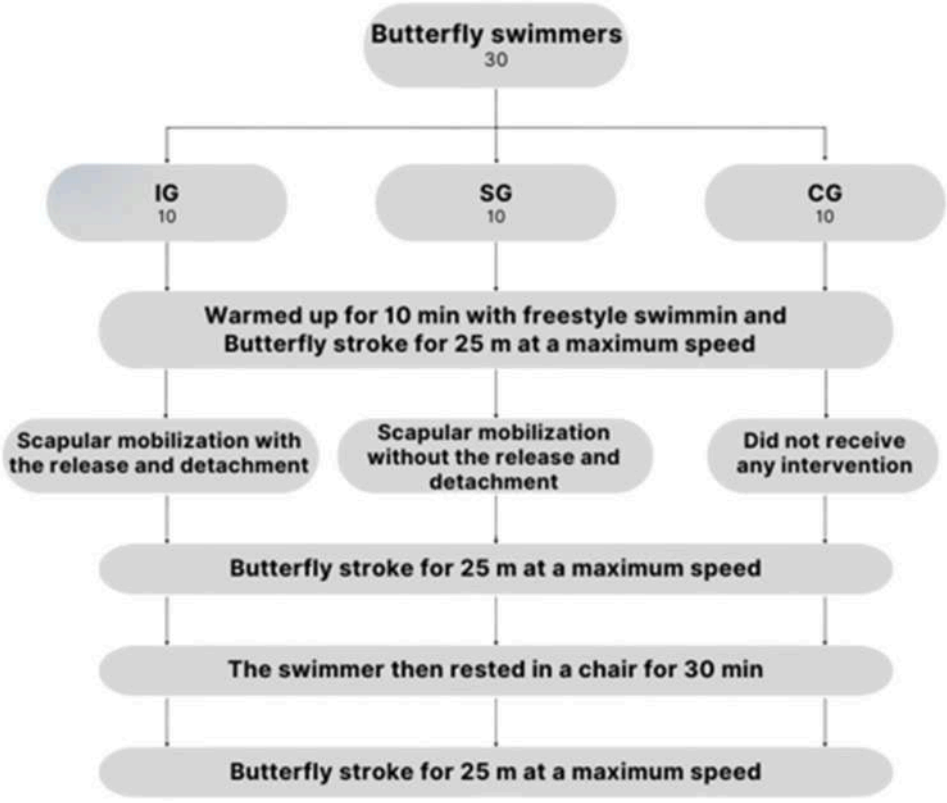

Fig. 3. Data collection procedure.

Table 1
Mean values, standard deviations (SD) and relative percentage frequency of data from the swimmers' evaluation form in the Control Groups (CG; n = 10), Intervention Group (IG; n = 10) and Sham Group (SG; n = 10).

Item	Group		
	CG	IG	SG
	Mean (SD)	Mean (SD)	Mean (SD)
Age (years)	16 (2.21)	16 (4.38)	13 (1.08)
Age started competitive swimming (years)	13 (2.56)	9.5 (3.65)	10 (2.62)
Height (m)	174.5 (8.73)	173.5 (8.35)	169 (8.19)
Weight (Kg)	69 (10.16)	68.15 (10.18)	54.8 (8.19)
Dominant hand; right (R) and left (L)	100% R	90% R 10% L	100% R
Breathing side in swimming	60% R 20% L 20% R/L	40% R 40% L 20% R/L	50% R [20% L 30% R/L
Level of competition	40% local 60% national	30% local 60% national 10% international	50% local 30% national 20% international
Swimming preference	50% crawl 20% freestyle and breaststroke 10% butterfly 10% butterfly and freestyle 10% breaststroke	20% all 20% freestyle 20% butterfly and freestyle 10% butterfly 10% backstroke and breaststroke 10% backstroke and freestyle 10% butterfly, freestyle and backstroke	30% backstroke and freestyle 20% freestyle 20% backstroke 20% butterfly and freestyle 10% butterfly
Competitive distance	10% 50 m, 100 m 50% 200, 400 m 10% 800 m, 1500 m 30% All	30% 50 m, 100 m 40% 200, 400 m 10% 800 m, 1500 m 20% All	20% 50 m, 100 m 50% 200, 400 m 10% 800 m, 1500 m 20% All
Number of weekly workouts	6 (0.32)	5 (1.20)	6 (0.84)
Distance per training (m)	5000 (0)	5000 (19,676,55)	5000 (0)
Distance per week of training (m)	30,000 (1581.14)	24,500 (19464.93)	30,000 (4216.37)
% swimming training (m)	181.5 (10.69)	184 (11.74)	177 (6.50)

Shapiro-Wilk test. Two-way repeated measures analysis of variance (ANOVA) with Bonferroni correction was used to verify the effect of the conditions before mobilization, immediately post mobilization, and post-late mobilization among the different groups (control groups; intervention group; sham group) in the performance of swimmers. For all analyses, a significance level of 5% was considered.

3. Results

The anthropometric and clinical characteristics of the participants' evaluation forms are shown in Table 1.

Although the sham group had lower age, height, and mass compared to the control and intervention groups, there was no significant difference between groups in the baseline evaluation (before mobilization) in all variables ($p > 0.05$).

The mean velocity (MV), stroke frequency (SF), and stroke length (SL) of the CG, IG, and SG are presented in Table 2. No statistically significant differences were found between the conditions or the interaction groups × conditions. Compared to the CG and IG, the SG showed significant differences in MV ($p = 0.002$; $p = 0.02$, respectively), SF ($p = 0.002$; $p = 0.003$, respectively), and SL ($p = 0.01$; $p = 0.05$, respectively).

4. Discussion

This study aimed to evaluate the acute effect of scapular mobilization with associated myofascial release compared to scapular mobilization without myofascial release on butterfly stroke sports performance. The findings showed that efficiency indicators were worse in the group that received scapular mobilization without myofascial release and detachment from the rib cage (SG) than in the group that received scapular mobilization with myofascial release and detachment from the rib cage (IG) and the group that did not receive any intervention (CG).

The mobilization applied in the SG may be responsible for the results observed, because it does not respect the direction of muscle fiber, the tissue limit, and because there is no detachment from the scapula. Therefore, caution should be exercised in the application of this technique in swimmers due to the negative influence on their sports performance. On the other hand, the mobilization whose maneuver was performed in the direction of muscle fibers, as in the IG, respecting the tissue limit during the detachment of the rib cage scapula, as well as the response of collagen tissue during mobilization did not positively or negatively influence performance (DiGiovanna et al., 1997; O'Sullivan and Schmitx, 2010; Smith, 2007; Sung et al., 2005). Thus, a single application of mobilization is not sufficient to trigger an increase or decrease in stroke speed, frequency, or length.

Published reports state that a decrease or maintenance of SF and an increase in SL represent a higher propulsive efficiency, leading to an increase in MV and a lower expenditure on the energy required for swimming (Caputo et al., 2000; Castro et al., 2005; Gatti et al., 2004; Maglischo, 1999; Yanai, 2003). Furthermore, Pelarigo et al. (2007) verified the effect of aerobic performance on the relationship between SF, SL, and stroke index corresponding to the maximum speed in 30 s of swimming, and found that higher swimming speeds are associated with higher SF.

The difference found in the SF values obtained in this study can be partially explained by the lower level of performance, as the swimming speed corresponds to the product of SF and SL. In our study, there was an increase in speed, an increase in SF, and a decrease in SL in the SG, indicating a worse swimming performance.

Some studies suggest that the reduction in SL observed during a test is related to the lower ability to develop strength to overcome resistance to movement, that is, worse performance (Craig et al., 1985; Craig and Pendergast, 1979). Even in highly trained swimmers, the improvement in SF has also been associated with increased yield (Huot-Marchand et al., 2005). The swimming speed represents the product of SF and SL (Hughson et al., 1987; Smith et al., 2002); thus, to maintain a given speed, swimmers generally adopt a combination of stroke rate and SL that they think is the most efficient. However, according to Dekerle et al. (2002) elite swimmers adopt different combinations of these parameters compared to less experienced swimmers, and this may be one of the factors that determine their highest levels of performance.

Craig et al. (1985) and Pelayo et al. (1996) analyzed the characteristics of stroke during a competition, using specialist athletes at each distance, and obtained a higher SF than those found in our study. This difference can be explained by the ability of the specialist swimmers to perform a greater number of strokes with a better application of strength and a better alignment of the body, which is important in minimizing drag and reducing fatigue. In the same study, Pelayo et al. (1996) demonstrated that anthropometric factors, such as height and arm span, can interfere with these indicators, that is, taller swimmers perform longer strokes at any test distance.

In the present study, the average heights in the CG, IG, and SG were 174.5 m (±8.73), 173.5 (±8.35), and 169 (±8.19), respectively, which is in agreement with published data for athletes of this age group (13–16 years) (Lima et al., 2001; Schneider and Meyer, 2005). Furthermore, our results coincide with those of Fernandes et al. (2002) who reported that swimmers' height increases with age; older swimmers are taller than younger swimmers, and these increases are related to the biological

Table 2
Mean values, standard deviations (SD), confidence Intervals (95% CI) and variance analyses obtained in the performance of swimmers after manual therapy, divided into Control Group (CG; n = 10), Intervention Group (IG; n = 10) and Sham Group (SG; n = 10) in different conditions before mobilization (BM), immediate post mobilization (IPM) and post-late mobilization (PLM).

Group										
		CG (A)		IG (B)		SG (C)		BG	BC	Interaction BG x BC
	Condition	Mean (SD)	CI 95%	Mean (SD)	CI 95%	Mean (SD)	CI 95%	p	p	p
Mean velocity (m/s)	Before mobilization	1.63 (0.19)	1.49–1.76	1.57 (0.19)	1.43–1.70	1.50 (0.21)	1.35–1.64	0,002	NS	NS
	Immediate post mobilization	1.60 (0.21)	1.45–1.75	1.55 (0.16)	1.43–1.66	1.40 (0.17)	1.28–1.52	CxA (p = 0.002)		
	Post-late mobilization	1.62 (0.18)	1.49–1.75	1.58 (0.18)	1.45–1.71	1.41 (0.17)	1.28–1.54	CxB (p = 0.02)		
Stroke frequency	Before mobilization	0.90 (0.11)	0.82–0.98	0.92 (0.14)	0.82–1.02	0.94 (0.11)	0.86–1.02	0,001	NS	NS
	Immediate post mobilization	0.90 (0.10)	0.83–0.97	0.93 (0.11)	0.85–1.01	0.85 (0.09)	0.79–0.91	CxA (p = 0.002)		
	Post-late mobilization	0.91 (0.01)	0.84–0.98	0.96 (0.11)	0.88–1.04	0.88 (0.08)	0.82–0.93	CxB (p = 0.003)		
Stroke length	Before mobilization	2.11 (1.03)	1.36–2.84	1.72 (0.22)	1.56–1.87	1.60 (0.12)	1.51–1.68	0,01	NS	NS
	Immediate post mobilization	1.77 (0.21)	1.62–1.92	2.12 (1.38)	1.13–3.10	1.65 (0.16)	1.54–1.77	CxA (p = 0.01)		
	Post-late mobilization	1.77 (0.21)	1.62–1.92	1.65 (0.16)	1.53–1.76	1.62 (0.25)	1.44–1.80	CxB (p = 0.05)		

Group-to-group and cross-conditions were determined using analysis of variance with Bonferroni adjustment. p = significance level; BG, between groups; BC, between conditions; NS, not significant.

development associated with age.

Farah et al. (2010) performed a descriptive analysis of the performance of three professional athletes in the women's 100-m freestyle, based on the variables SL, SF, and MV, and observed that athletes with the highest speed had the highest SL and SF. Grimston and Hay (1986) evaluated 12 competitive swimmers from an American university team, their results indicated that SL correlates with SF. Furthermore, data from the literature suggest that higher swimming speeds are associated with higher SF (Huot-Marchand et al., 2005; Keskinen and Komi, 1993; Pelayo et al., 1996).

The functionality of the upper limb depends on the mobility of the thoracic scapular joint (Beach et al., 1992; McClure et al., 2004; Thomas et al., 2007; Wang et al., 1999). Some studies have shown that abnormal patterns of scapular movements need to be normalized to restore the biomechanics of the shoulder complex (Brand, 2008; Hallaçeli et al., 2006; Thomas et al., 2007; Vermeulen, 2002); otherwise, these dysfunctions can trigger injuries (Cools et al., 2003; da Silva et al., 2015; Kibler et al., 2002; McClure et al., 2004). Accordingly, Meliscki et al. (2011) stated that the training load is related to alterations in scapular positioning. In addition, supraspinal tendinopathy correlates positively with the time of sports practice and the distance covered by weekly training (Aguiar et al., 2010; Sein et al., 2007, 2010; Venâncio et al., 2012). In the present study, the variable mean distance swam per week of training in the CG, IG, and SG was 30,000 m, 24,500 m, and 30,000 m, respectively. These distances are in line with the findings of high-performance swimmers (Dekerle et al., 2002), indicating that our sample was composed of elite swimmers with a high training load.

Age was not an important factor in triggering any pathology in the shoulder complex, since the mean age was 16 years in the CG, 16 years in the IG, and 13 years in the SG. In other words, the time of sports practice (CG, 13 years; IG, 9.5 years; and SG, 10 years) was not responsible for injuries in the swimmers in this study.

In addition to the number of sessions, associating manual therapy with specific exercises can be a beneficial strategy for future studies in this population. Bang and Deyle (2000) evaluated 30 men and 20 women diagnosed with shoulder impact syndrome, divided into two groups: the first group performed flexibility and strength exercises, and the second group performed the same exercises associated with manual therapeutic management; they found that manual therapy combined with exercise is more effective in pain reduction. Additionally, Almeida et al. (2011) applied a 24-session protocol, composed of myofascial release in the cervical, thoracic, and scapulohumeral joints, to treat the shoulder of only one swimmer, and concluded that at the end of the sessions, there was a reduction in pain and improved functionality.

According to Paine and Voight (2013) the importance of scapular positioning in the functionality of the upper limb has only been studied in recent decades. Although several articles on manual therapy treatment of the shoulder complex have been published, only two involved swimmers. In addition, to date, this is the first article that evaluates the effectiveness of manual therapy in the sports performance during butterfly swimming. Because our findings showed that only one application does not sufficiently influence the indicators of sports performance in this swimming modality, further studies in this area are suggested, as well as studies that can propose a methodology with a greater number of scapular mobilization interventions with release of the rib cage and incorporated into sports training.

The limitations of the studies are related to the sample size, the risk of non-probabilistic contraction bias and the lack of blinding of the evaluators. Thus, the results of this study should be evaluated with caution.

5. Conclusion

Our results liked that although the sham group had lower age, height and mass compared to the control and intervention groups, there was no significant difference between groups at baseline in all variables. Still, there were no statistically significant differences between conditions or the groups × conditions interaction. However, compared to the CG and IG, the group that received manual therapy through scapular release without myofascial release associated with detachment of the scapula

from the rib cage worsened the indicators of swimming efficiency (stroke frequency, length, and mean speed) even 30 min after the application of the technique. Caution must be used when applying these results in practice.

Clinical relevance

Findings: The findings showed that efficiency indicators were worse in the group that received scapular mobilization without myofascial release and detachment from the rib cage than in the group that received scapular mobilization with myofascial release and detachment from the rib cage and the group that did not receive any intervention.

Implications: Manual therapy through scapular mobilization without associated myofascial release worsened the swimming efficiency indicators, even 30 min after the application of the technique.

Caution: Caution is recommended when using techniques with little or no evidence as they may reduce the sports performance of swimmers.

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CRediT authorship contribution statement

Tamiris Beppler Martins: Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Tais Beppler Martins:** Visualization, Supervision. **Gustavo Soares Pereira:** Supervision, Methodology, Formal analysis, Data curation. **Larissa Milani Brognoli Sinhorim:** Visualization, Supervision, Methodology. **Suzana Matheus Pereira:** Visualization, Validation, Supervision, Methodology. **Gilmar Moraes Santos:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Fascia Science and Clinical Applications

Acute effects of myofascial reorganization on trapezius muscle oxygenation in individuals with nonspecific neck pain

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ABSTRACT

Background and purpose: Nonspecific neck pain (NNP) is a common idiopathic disorder in the general population that affects the trapezius muscle (TM) and blood supply, thereby compromising the fascial system. Myofascial reorganization (MR) is a physical therapy technique that can influence the dynamics of local fluids reducing excessive muscle tension and capillary constriction, and increasing local blood flow. This study aimed to investigate whether MR improves peripheral muscle oxygenation.
Methods: This was a quasi-experimental study with an intentional non-probability sample. Fifty participants (women: 36, men: 14) with and without NNP were assigned to either the experimental group (EG: n = 25, with NNP, subjected to MR) or the control group (CG: without NNP, no MR intervention). TM oxygenation was measured using near-infrared spectroscopy (NIRS) before and after a single intervention. All participants were evaluated and reassessed after 10 min.
Results: The results revealed that immediately after 10 min of MR, the EG exhibited an increase in the oxyhemoglobin level of the medium fibers of the TM (0.72 ± 1.47 *vs.* −0.14 ± 1.33 mmol/dL, p = 0.01). In addition, functional disability (CG: 5.48 ± 5.58%/EG: 21.12 ± 7.73%) and neck pain were measured using the neck disability index. The pain pressure threshold (CG: 70.49 ± 32.29 kgf/EG: 51.08 ± 27.65 kgf) and pain intensity (CG: 0.76 ± 1.56/EG: 3.28 ± 2.35) were also measured.
Conclusion: The findings indicate that application of MR for 10 min increases the tissue oxyhemoglobin level in the TM of the group with NNP compared to the CG without NNP.
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1. Introduction

Nonspecific neck pain (NNP) is a common idiopathic disorder that occurs in the general population, with a high prevalence in the occupational sector (Hogg-Johnson et al., 2008). The prevalence increases with age up to 70–74 years and occurs more frequently in women (Safiri et al., 2020). In addition, NNP was ranked as the fourth highest contributor to disability (March et al., 2014).

One cause of this dysfunction is the incorrect execution of shoulder movements that depend on scapular stabilization during daily activities (Park and Lee, 2020). The scapular movement involves participation of the lower and middle fibers of the trapezius muscle (TM) (Stapait et al., 2013). Almost half of a muscle's longitudinal stress is transmitted to the fascia (Findley and Shalwala, 2013). In addition, during some activities that generate muscle overload, the fascia may suffer energy demands in which the local blood supply can be reduced (Boushel et al., 2001). It is possible that these changes in the energy demands affect the fascial system, limiting or preventing the proper sliding of the tissues, resulting in

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NNP.

Physiotherapy treatments for neck pain involve exercise and manual therapy. In manual therapy, myofascial reorganization (MR) can be used, which involves support, manual pressure, and slips in the myofascial tissue, contributing to extracellular matrix remodeling, homeostasis of inflammatory cytokines, and analgesic effects (Amorim et al., 2018; Sinhorim et al., 2019; França et al., 2020). According to Schleip et al. (2005), interventions directed at fascial systems, such as MR, can stimulate mechanoreceptors inside the fascia, contributing to changes in the dynamics of local fluids, reducing excessive muscle tension and capillary constriction, and increasing local blood flow.

In addition, it is a technique that uses only manual contact, considered a simple method, often reversible and non-invasive, non-pharmacological, low cost, and easily applicable in clinical practice. It is important to evaluate the clinical effects of muscle oxygenation for the treatment of NNP using MR, which could provide new information and impact potential implementation in the clinical environment. We hypothesized that intervention with MR could modify muscle oxygenation after a single application. Therefore, the aim of this study was to investigate the acute effect of MR on peripheral muscle oxygenation in TM.

2. Methods

2.1. Study design

This was a quasi-experimental study with an intentional non-probability sample. Individuals with and without neck pain were investigated. The experimental group (EG), with NNP, was subjected to MR intervention for 10 min and evaluated before and after treatment. The control group (CG), without NNP, was evaluated before and after 10 min without any intervention. Both were assessed using the same evaluators. The primary outcome was the peripheral muscle oxygenation. The study was approved by the Human Research and Ethics Committee of Universidade do Estado de Santa Catarina (number: 2.630.855) and Clinical Trials Record NCT03882515. Individuals who agreed to participate in the research signed an informed consent form.

2.2. Subjects

Volunteers aged 18–35 years, with or without NNP, were included after consent was provided. NNP was defined as mild pain (0–2 visual analog scale [VAS] for pain) in the TM during daily or work activities. Individuals with NNP self-reports in the last three months without a definite cause were included.

In addition, they should have at least “mild” pain in session 1 based on the Neck Disability Index (NDI). For the participants without NNP, the NDI should be zero and they were paired with the EG according to age, sex, and body mass index (BMI). The exclusion criteria for both groups were neurological diseases, history of trauma or surgery on the cervical spine, clinical diagnosis of hernias or nerve compressions, metabolic diseases or other comorbidities and previous physiotherapeutic treatment within the previous three months.

2.2.1. Sample calculation

The number of participants required for each group was estimated using the G*Power 3.0.10 software using two-tailed post hoc power analysis with *t*-test difference between the two independent means. Using these parameters, a total sample of 50 participants (25 per group) provided 79% power and an effect size of 0.80.

2.3. Outcome measures

The primary outcome was the peripheral muscle oxygenation. It was measured using near-infrared spectroscopy (NIRS) (Artinis Medical Systems, 2017).

The secondary outcomes were pressure-pain thresholds and pain intensity. They were evaluated using a pressure algometer (Jtech Medical Industries, 2017) and the VAS, respectively. In addition, functional disability and neck pain were evaluated using the NDI questionnaire (Vernon and Mior, 1991), validated for the Portuguese language by Cook et al. (2006).

2.4. Data collection procedures

The evaluation and intervention were conducted in a room with controlled temperature (24 °C) at the Biomechanics Laboratory of Universidade do Estado de Santa Catarina. After the anthropometric measurements, the participant was placed in a prone position on a stretcher, and muscle oxygenation of the TM was measured. The skin was cleaned with alcohol, and the device was positioned bilaterally in the middle fibers of the TM. For the optode position, the recommendations of SENIAM (Surface ElectroMyoGraphy for the Non-Invasive Assessment of Muscles) were used to identify the muscle belly of the middle fibers of the right and left trapezius muscles. If hair was present, trichotomy was performed using individual disposable blades for each subject. Individuals wore swimsuits so as not to alter the data collected by the optode or to hinder application of the technique. In addition, the equipment was covered with black cloth to prevent light penetration. The acquisition frequency was 10 Hz, and the measurements lasted for 1 min. Muscle oxygenation was measured before the MR intervention for the EG and 10 min after MR. For the CG, without NNP, and without any intervention, the muscle oxygenation was measured and assessed after 10 min.

Following this measurement, the NDI questionnaire and VAS scoring system were applied, and the pressure-pain thresholds were measured. The same positioning of the NIRS optode on the TM belly was used for the algometer measurements. Pressure was applied perpendicular to the skin until the maximum pain endured by the subject was recorded; the procedure was repeated twice on each side. The measurements were performed by the same evaluator.

2.5. Intervention

The MR protocol followed the study by Sinhorim et al. (2019). Manipulation techniques aim to emphasize shear loading, tensile loading, and compressive loading of the fascial system. The specific manual treatment used in this study can be described as a manual connective tissue manipulation that is similar to the Rolfing method (França et al., 2020). The MR protocol has 11 steps, which are illustrated in Fig. 1.

2.6. Data analysis and statistics

Tissue oxygenation data were provided by dedicated software (Oxysoft®, Artinis, Netherlands) for the muscle oxygenation variables (oxyhemoglobin, deoxyhemoglobin, total hemoglobin, and tissue saturation index). The averages of the variables during 1 min of data collection were calculated, and the variation (delta) between the baseline and after 10 min was evaluated for both groups.

Pain tolerance data were obtained using the equipment itself, which was averaged from two collections bilaterally. The NDI questionnaire was extracted from the index score of each participant at the time of collection.

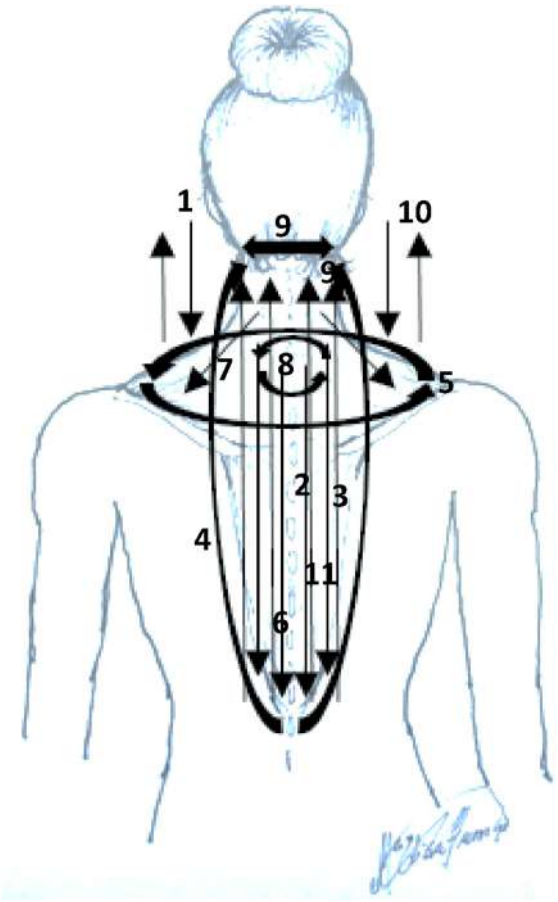

Fig. 1. Scheme of the performed MR protocols in the trapezius muscle (Sinhorim et al., 2019). MR, myofascial reorganization; 1) patient in side position (SP). Pressure with closed fist and movement in half moon in the medium fibers of the trapezius muscle (TM). From steps 2 to 9, the patient is in the prone position (PP). 2/3) Sliding along the TM to the base of the skull 4) Sliding of the T12 level around the lateral edge of the scapula to the axilla. 5) Sliding forming a canoe from one acromion to another passing above and below the level of T1. 6) The tenar region slides in the caudal direction from the upper TM to the lower TM. 7) Sliding between the proximal and distal insertion of TM media fibers. 8) Sliding around the T1 spinous process. 9) Transverse sliding at the upper insertion of the upper TM fibers. 10) Patient in the supine position (SP). Tweezer traction of the TM fibers. 11) Patient in a seated position. Perform continuous clamping and sliding on the TM with the hands in a fist.

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS v. 20.0). The normality assumption was assessed using the Kolmogorov-Smirnov test. Student's t-test for independent samples was used for comparison between the groups. The level of significance was set at $P \leq 0.05$.

3. Results

Fifty subjects were evaluated between August 2018 and June 2019 (women: 36, men: 14). As shown in Table 1, the groups were matched by age and BMI and differed regarding pain tolerance and NDI, which reinforces the different characteristics between groups with and without NNP.

The muscle oxygenation variables analyzed in this study are presented in Table 2. The findings reveal that the participants subjected to the MR treatment protocol exhibited an increase in oxyhemoglobin (0.72 μMol/L) compared to subjects without the intervention (- 0.14 μMol/l). This difference was statistically significant ($t = -2.69$; $p < 0.01$) (Table 2).

The pressure-pain thresholds EG was 51.08 ± 27.65 kgf, while the CG was 70.49 ± 32.29 kgf. In the pain intensity, the EG showed media of 3.28 ± 2.35 VAS and the CG of 0.76 ± 1.56 VAS. In functional disability, the EG showed 21.12 ± 7.73%, and the CG 5.48 ± 5.58%.

Table 1
Demographic and clinical variables in groups with (EG) and without (CG) nonspecific neck pain.

Variables	EG (n = 25)	CG (n = 25)	p-value
Age (years)	22.60 ± 3.85	22.64 ± 3.80	0.97
Mass (kg)	67.00 ± 14.78	65.20 ± 11.52	0.63
Height (m)	1.67 ± 0.08	1.67 ± 0.08	0.98
BMI (kg/m^2)	23.84 ± 4.78	23.14 ± 2.50	0.49
Pain (kgf)	51.08 ± 27.65	70.49 ± 32.29	0.02*
Pain (VAS)	3.28 ± 2.35	0.76 ± 1.56	0.00*
NDI (%)	21.12 ± 7.73	5.48 ± 5.58	0.00*

EG, experimental group: myofascial reorganization group; CG, control group; BMI, body mass index; NDI, neck disability index. *p ˂ 0.05, paired Student's t-test for independent variables.

Table 2
Mean and standard deviation values for the variation of oxyhemoglobin, deoxyhemoglobin, total hemoglobin and tissue saturation index (TSI) in the middle fibers of the trapezius muscle for the groups with (EG) and without (CG) nonspecific neck pain.

Variables	EG	CG	p-value
ΔO_2Hb (μmol/L)	0.72 ± 1.47	−0.14 ± 1.33	0.01*
ΔHHb (μmol/L)	0.09 ± 0.77	1.72 ± 6.16	0.21
ΔtHb (μmol/L)	0.73 ± 2.53	−0.12 ± 2.01	0.09
ΔTSI (%)	3.56 ± 4.95	1.83 ± 3.65	0.25

EG, experimental group: myofascial reorganization group; CG, control group; ΔO_2Hb, change in oxyhemoglobin concentration; ΔHHb, change in deoxyhemoglobin concentration; ΔtHb, change in total hemoglobin; ΔTSI, change in tissue saturation index.

4. Discussion

This study investigated whether MR acutely modifies variables related to peripheral muscle oxygenation of the medium TM fibers in individuals with NNP.

The results revealed that immediately after treatment, the EG exhibited an increase in oxyhemoglobin in the medium fibers of the TM, after 10 min of application of MR (0.72 ± 1.47 *vs* −0.14 ± 1.33 Mmol/dl, $p = 0.01$). In addition, the findings of pain tolerance using the NDI questionnaire reinforce the differences between the groups with and without NNP.

Pain can cause tissue hypoxia (Cagnie et al., 2012). The subjects with NNP in this study displayed these characteristics, based on the qualitative and quantitative assessments of pain. The high NDI scores of the EG compared to those of the CG also corroborate these findings. Daily life activities can generate postural overload in the TM, which makes the fascia tissue rigid and dense, generating adhesions and pain.

According to Barão et al. (2011), Rodrigues-Bigaton et al. (2014), and Filho (2016), individuals with myofascial disorders have increased intramuscular pressure and mechanical compression of the vessels that supply the TM. These changes can be caused by the presence of myofascial adhesions (Prentice, 2011), which decrease the blood supply to the muscle. Larsson et al., 2000 and Rodrigues-Bigaton et al. (2014), reported that this change in perfusion causes consequent inefficiency of aerobic metabolism (decreased oxygenation), and anaerobic metabolism is then used by the body, resulting in a greater propensity for muscle fatigue (Bron and Dommerholt, 2012). During application of the MR technique, the release of the soft tissues resulted in an increase in local

oxygenation, as demonstrated in this study, evidenced by the increase in oxyhemoglobin.

Symptomatic participants were university students with overactivated TM at rest due to postural overload imposed by long hours in the sitting position. Performing movements involving the TM can trigger a decrease in muscle oxygenation, as noted in the study by Elcadi et al. (2014), who investigated oxygenation in the TM during a 5-min low-intensity contraction (10%). The authors observed a significant decrease in oxygenation during the contraction. In accordance with the same results (Flodgren et al., 2009 and Flodgren et al., 2010), investigated the tissue saturation index (TSI) in the middle third of the upper TM using NIRS and observed a reduction from 83.1% to 77.4% during repetitive work. However, Schah et al. (2017) reported increased oxygenation of the lumbar paravertebral musculature of asymptomatic individuals 30 min after applying MR. Perhaps the reduced application time of MR in this study resulted in only a modest change in the TSI compared to that in the CG.

Changes can be caused by the presence of myofascial adhesions (Prentice, 2011), which decrease the blood supply to the muscle. Schleip et al. (2019) reported that muscle spindle sensitivity is influenced by the stiffness of the perimysial connective tissue. Based on the influence of spindle-derived mechanosensation on alpha motor neuron activation, this interaction may contribute to active muscle tonicity (Giuriati et al., 2018).

MR is a technique that enables readjustment of these structures, thus facilitating an increase in oxygenation immediately after application. Our results support this premise, because MR significantly altered tissue oxyhemoglobin and, consequently, more oxygen to the TM was observed as an acute effect of the technique. In addition, it influences the receptors present in the fascia, contributing to changes in the dynamics of local fluids, capillary constriction, and increased local blood flow, making the cellular medium more pro-resolutive, thereby restoring the normal integrity of the treated tissue (Sinhorim et al., 2019; França et al., 2020).

The longitudinal application of the MR protocol, with a sequence of visits, should provide long-term effects of MR to the local microcirculation and quality of life of individuals with NNP.

This study has some limitations. External variables that were not fully controlled could have influenced the results. Among these, the use of medications, physical activity on the day of collection, and stress levels could have impacted the results because our sample mainly consisted of undergraduate students. In addition, the menstrual cycle (Clark et al., 2010) in female participants and caffeine intake on the day of the intervention (Martins et al., 2013) were not evaluated.

5. Implications for physiotherapy practice

NNP is a common condition that affects a considerable proportion of the economically active population. Manual techniques, such as manipulation of the fascial system, are widely used, but poorly understood. They aim to improve neuromusculoskeletal tissue, promote greater sliding between tissues, and lower energy expenditure during the performance of activities of daily living. When applied to asymptomatic individuals as performed in this study, there is a potential prophylactic effect. Elucidating the actual effects of manual intervention is vitally important. MR is a technique focused on the fascial system and applies a specific mechanical stimulus on connective tissue, thereby promoting the response of this tissue. It was not clear if MR could obtain an immediate result following its application in the orthopedic condition involving NNP. Our findings revealed that MR had an immediate effect on peripheral muscle oxygenation. The search for safe, non-pharmacological, low-cost, and relatively simple rehabilitation strategies can provide professionals in clinical practice with options that are reliable and effective in improving outcomes for individuals.

In conclusion, the acute effects of MR after 10 min of application revealed that there was an increase in oxyhemoglobin in the middle fibers of the TM, when compared to a CG without NNP. Although long-term results have not been evaluated, it is believed that continued application of the protocol will provide enhanced results over time, resulting in long term benefits.

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Declarations of conflict of interest

None.

CRediT authorship contribution statement

Mayane dos Santos Amorim: literature review, data collection, Formal analysis, final edition. **Larissa Sinhorim:** literature review, Formal analysis, final edition. **Janaína Wagner:** data collection. **Francisco de Paula Lemos:** data collection. **Robert Schleip:** final edition. **Anelise Sonza:** data collection, Formal analysis, final edition. **Gilmar Moraes Santos:** Formal analysis, final edition.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jbmt.2021.10.010.

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Analgesia by fascia manipulation is mediated by peripheral and spinal adenosine A_1 receptor in a mouse model of peripheral inflammation

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ABSTRACT

The role of adenosine receptors in fascial manipulation-induced analgesia has not yet been investigated. The purpose of this study was to evaluate the involvement of the adenosine A_1 receptor (A_1R) in the antihyperalgesic effect of plantar fascia manipulation (PFM), specifically in mice with peripheral inflammation. Mice injected with Complete Freund's Adjuvant (CFA) underwent behavioral, i.e. mechanical hyperalgesia and edema. The mice underwent PFM for either 3, 9 or 15 min. Response frequency to mechanical stimuli was then assessed at 24 and 96 h after plantar CFA injection. The adenosinergic receptors were assessed by systemic (intraperitoneal, i.p.), central (intrathecal, i.t.), and peripheral (intraplantar, i.pl.) administration of caffeine. The participation of the A_1R was investigated using the 1,3-dipropyl-8-cyclopentylxanthine (DPCPX), a selective A_1R subtype antagonist. PFM inhibited mechanical hyperalgesia induced by CFA injection and did not reduce paw edema. Furthermore, the antihyperalgesic effect of PFM was prevented by pretreatment of the animals with caffeine given by i.p., i.pl., and i.t. routes. In addition, i.pl. and i.t. administrations of DPCPX blocked the antihyperalgesia caused by PFM. These observations indicate that adenosine receptors mediate the antihyperalgesic effect of PFM. Caffeine's inhibition of PFM-induced antihyperalgesia suggests that a more precise understanding of how fascia-manipulation and caffeine interact is warranted.

Introduction

The effect of mechanical forces on the human body is a topic of high interest both for scientists who study neural systems involved in mechanosensation, and for clinicians who use force-based manipulations such as manual therapy, including spinal manipulation or acupuncture, with the overall aim of treating health problems (NIH). Manual therapy is considered one of the oldest interventions in medicine and can be described as a practice of passive movement and application of mechanical forces in joints and soft tissues (Chaudhry et al., 2008). Fascia manipulation is a common approach used in manual therapy (Simmonds et al., 2012) and its clinical effectiveness in reducing back pain in patients with scoliosis has been demonstrated in a systematic review (López-Torres et al., 2021) alongside pressure pain thresholds (Ajimsha et al., 2014; Bakar et al., 2014; Celenay et al., 2016). Fascia manipulation has also proved efficacious in treating cervical pain (Bakar

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et al., 2014; Dos Santos et al., 2024; Dos Santos et al., 2022) pain at night and scores related to quality of life (Celenay et al., 2016). Another systematic review study showed that manual fascia therapy improves pain and function in patients with plantar fasciitis, with a 1A level of evidence for treatment (Fraser et al., 2018).

One basis for these studies is the demonstration that manual therapy produces antinociceptive actions in nociceptive, inflammatory, and neuropathic pain models (França et al., 2020; Martins et al., 2012; Martins et al., 2013; Martins et al., 2013; Martins et al., 2011; Omura et al., 2022; Salgado et al., 2019). Several actions at the cellular level could contribute to manual therapy's neural mechanisms in these models, which include the release of neurotransmitters as well as the interactions within receptors (Martins et al., 2012; Martins et al., 2013; Martins et al., 2013; Salgado et al., 2019) between the adenosine A_1R (Martins et al., 2013). In support of the involvement of adenosine, initially, Goldman et al. (Goldman et al., 2010) showed through microdialysis in mice that manipulation (swivel) of an acupuncture needle inserted into the subcutaneous tissue resulted in a sustained local release of adenosine triphosphate, adenosine diphosphate and adenosine. Furthermore, injection of a selective A_1R agonist into mice produced a transient antinociceptive effect, similar to that of acupuncture. Finally, analgesic effects produced by either manipulation of the acupuncture needle or by the A_1R agonist were prevented in A_1R knockout mice. Subsequently, our research group demonstrated that caffeine, a non-selective A_1R and A_2 receptor (A_2R) antagonist, and the DPCPX, a selective A_1R antagonist (relative when following intraplantar, or i.pl., intrathecal, or i.t. administration), inhibited the antihyperalgesic effect produced by ankle joint mobilization (Martins et al., 2013). Thus, activation of the A_1R could also be a plausible explanation for the neural mechanism of the analgesic effect of manual fascia therapy; this is supported by A_1R's documented involvement in the suppression of pain transmission at various neuraxial levels (peripheral, spinal, supraspinatus) (Sawynok, 1998; Sawynok and Liu, 2003), and that treatments involving mechanical manipulation of joints and muscles may also be associated with an efflux of cytosolic ATP sufficient to elevate extracellular adenosine, as suggested by Goldman et al. (Goldman et al., 2010).

Caffeine is recognized as a stimulant on the central nervous system and is consumed worldwide (Reyes and Cornelis, 2018), and its pharmacological actions are mainly attributed to the blockade of receptor adenosine 1 (A_1R), receptor adenosine 2A ($A_{2A}R$), receptor adenosine 2B ($A_{2B}R$), with a lower affinity for the receptor adenosine 3 (A_3R) and adenosine as the main endogenous ligand of these receptors (Sawynok, 2011). The most clinically important fact for pain management is that caffeine, at doses lower than those implied in adjuvant analgesia, blocks antinociception by several therapeutic agents in clinical and preclinical studies. Thus, dietary caffeine may interfere with the analgesic actions of these agents such as acupuncture (Goldman et al., 2010) transcutaneous electrical nerve stimulation (Marchand et al., 1995), physical exercises (Martins et al., 2013) and joint mobilization (Martins et al., 2013).

Based on this evidence, we asked whether PFM could increase endogenous adenosine levels and produce antihyperalgesia through signaling via A_1R's. In the present study, we used a behavioral and pharmacological approach to determine: (1) the duration (time) of treatment with PFM that best reduces mechanical hyperalgesia, (2) whether caffeine, administrated through peripheral (paw) or central (spinal), prevents analgesia (antihyperalgesia) by PFM, and lastly (3) whether the antihyperalgesic profile of PFM is modified by DPCPX (also when administrated in peripheral and central sites).

Experimental procedures

Animals

All animal care and experimental procedures were carried out in accordance with the National Institutes of Health Animal Care Guidelines (NIH publications No. 80–23). The present study employed female Swiss mice (25–35 g) obtained from the Federal University of Santa Catarina (UFSC). Animals were housed under a 12-hour light/12-hour dark cycle (lights on at 6:00 a.m.) in a room with controlled temperature (22 ± 2 °C) and given food and water *ad libitum*. Animals were accustomed to the laboratory conditions for at least 1 h before testing. Experiments were performed between 8:00 am and 12:00 am.

Drugs

The following substances were used: Dimethyl sulfoxide (DMSO) (Merck, Darmstadt, Germany), dexamethasone (a steroidal anti-inflammatory drug, Aché Laboratórios Farmacêuticos S/A, Brazil) caffeine, N6-[2-(3,5 dimethoxyphenyl) 2(methylphenyl)ethyl] adenosine (Sigma Chemical Co., USA), DPCPX (Tocris Bioscience, Ellisville, MO) were dissolved in saline with 5 % DMSO. The final concentration of DMSO did not exceed 5 % and did not cause any effect *per se*. When drugs were delivered by intraperitoneal route, a constant volume of 10 mL/kg body weight was injected. When drugs were administered by intrathecal or intraplantar routes, a volume of 5 µl, or 20 µl, was injected, respectively. Appropriate control-treated groups were also assessed simultaneously. The doses of all substances used were chosen based on data in the literature or were selected from preliminary experiments conducted in our laboratory (Goldman et al., 2010; Martins et al., 2013; Sawynok and Liu, 2003; Sawynok and Reid, 2012).

Animal model of complete Freund's adjuvant (CFA)-peripheral inflammation

Peripheral inflammation was induced by a 20 µl right hindlimb intraplantar (i.pl.) injection of CFA − 50 % concentration solution dissolved in 0.9 % saline and Tween®80 (Fig. 1) (De Oliveira et al., 2021; Martins et al., 2016).

PFM treatment

Fascia treatment was performed using the Myofascial Reorganization® technique (De Oliveira et al., 2021; França et al., 2020) (Fig. 1). We carried out an adaptation of the protocol previously described by França et al. (França et al., 2020) which performed a translation of the treatment performed in humans to mice. The protocol was based on previous anatomical and dissection studies of the fascial complex in mice performed in our lab (data not published), with the objective of preserving the principles of the technique applied to humans, seeking to find the most adequate correspondence between the characteristics of human treatment when applied to mice. The animals were anesthetized with a 2 % isoflurane to 100 % oxygen ratio and positioned in the prone position; the physical therapist positioned the dorsal surface of the animal's right hind paw over the distal interphalangeal surface of the left hand, leaving the plantar surface of the paw exposed and free from tension. After the initial positioning, the physical therapist touched the animal's plantar fascia with the pulp of the 3rd finger of the right hand. After a few seconds of contact with the tissue, the technique was applied in two moments: i) sustained tensional loading of the plantar fascia, through a tangential traction in the craniocaudal direction and ii) micro movements latero-lateral describing a small curve 180 degrees that causes shearing of the animal's plantar fascia. The treatments were performed at separate times (3 min, 9 min, or 15 min) (Martins et al., 2012). Control treatment: After contact of the physical therapist's 3rd finger with the mouse's plantar fascia, mechanical traction and shear loads were not performed. The contact used was maintained at the same times as the original technique (França et al., 2020; Martins et al., 2012).

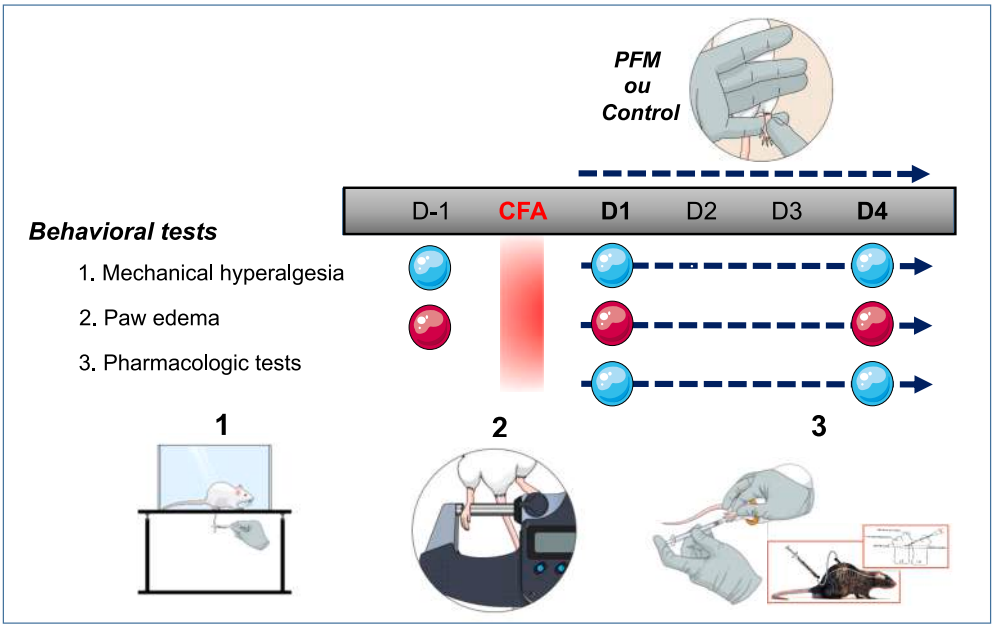

Fig. 1. Schematic representation of the experimental design. PFM, plantar fascia manipulation.

Measurement of mechanical hyperalgesia and paw edema

The mechanical hypersensitivity was measured as described previously (Martins et al., 2016). This test was carried out with the mice confined in glass cylinders (20 cm diameter) and an elevated wire mesh platform to allow access to the ventral surface of the hind paws. The right hind paw was stimulated with a constant pressure of 0.6 g von Frey filaments (Stoelting, Chicago, USA). The response frequency to 10 applications was taken as the nociceptive behavior. The response to mechanical stimulation (the number of paw withdrawals) was recorded and expressed as a percentage of the withdrawal response (Martins et al., 2016). Edema assessment was then performed by measuring the thickness of the right hind paw with a digital micrometer (Insize®, SP, Brazil). The results were expressed as the difference between the thickness of the right hind paw (submitted to CFA) and the baseline value (before the CFA procedure) of the same paw (Fig. 1). Evaluators were blinded to the groups evaluated during all tests.

To assess the effects of PFM on CFA-induced inflammatory pain and edema, animals were treated with PFM at 24 h and 96 h after CFA i.pl. injection (Fig. 1). Development of mechanical hyperalgesia was evaluated at 30 min, 1 h, and 2 h after treatment to verify the time course of PFM in reducing mechanical hyperalgesia (Martins et al., 2012) and 3 h after to edema. In this experiment, the following groups (n = 8) were used: (1) CFA+Control, (2) CFA+PFM 3 min, (3) CFA+PFM 9 min, (4) CFA+PFM 15 min, (5) CFA+Saline, (6) CFA+Dexamethasone.

Evaluation of the effect of caffeine administration on different pain modulatory sites on antihyperalgesic action caused by PFM

In order to assess the effect of caffeine on the antihyperalgesic action of PFM, the animals were pretreated with the caffeine by i.p. (10 mg/kg, 20 min prior), i.t. or i.pl. (150 nmol, 15 min prior) routes, before the PFM 9 min treatment at both 24 h and 96 h after CFA i.pl. injection. The choice of the doses and times of pretreatment were based on our previous data (Martins et al., 2013; Rittner et al., 2001; Sawynok, 2011). Mechanical hyperalgesia was then evaluated 30 min after the PFM 9 min treatment as described below. In this experiment, the following groups (n = 8) were used by different routes: (1) CFA+Saline + Control, (2) CFA+Caffeine + Control, (3) CFA+Saline + PFM 9 min, (4) CFA+Caffeine + PFM 9 min.

To determine the involvement of peripheral and spinal A_1Rs on the antihyperalgesia-induced PFM 9 min treatment, the animals received an i.pl. or i.t. injection of DMSO (5 µl/i.t.) or DPCPX (10 nmol/20 µl/i.t. and 10 nmol/5µl/i.t.), respectively. After 15 min, the animals received saline/DMSO or PFM 9 min treatment. Mechanical hyperalgesia was evaluated 30 min after treatments. In this experiment, the following groups (n = 8) were used by different routes: (1) CFA+Saline + Control, (2) CFA+DPCPX+Control, (3) CFA+DPCPX+PFM 9 min, (4) CFA+DPCPX+PFM 9 min.

Statistical analyses

The results are presented as mean plus standard deviation of the mean (SDM). Statistical significance of differences between groups was detected by two-way repeated measures (RM) analysis of variance (ANOVA) followed by Tukey post hoc test. P-values ($P<0.05$) were considered as indicative of significance. Statistics were calculated using Graph-Pad Prism 5.0 software (San Diego, CA, USA, 2009).

Results

Effects of different PFM treatment times on mechanical hyperalgesia

The results presented in Fig. 2 demonstrate that the injection i.pl. of CFA induced an increase in the frequency of paw withdrawal response (mechanical hyperalgesia) of mice when compared to baseline. Mechanical hyperalgesia in the animals' ipsilateral paw still persisted on day 4 (Fig. 2, A-D).

At 24 h after CFA i.pl. injection, two-way RM ANOVA revealed significant main effects of PFM treatment [$F(3, 28) = 10.87$; $P = 0.0001$] and time [$F(4,182, 117,1) = 91.43$; $P = 0.0001$] and treatment x time interaction [$F(15, 140) = 2.385$; $P = 0.0043$].

24 h after i.pl. of CFA, acute treatment with PFM for 9 min caused a significant reduction in mechanical hyperalgesia starting at 30 min ($P = 0.029$) and lasting for up to 1 h ($P = 0.0366$) after treatment. However, at 96 h after CFA i.pl. injection, two-way RM ANOVA revealed significant main effects of PFM treatment [$F(3, 105) = 14.07$; $P = 0.0001$] and time [$F(4, 35) = 6.417$; $P = 0.0006$] and treatment x time interaction [$F(12, 105) = 2.676$; $P = 0.0035$]. The treatments with PFM 3 min or PFM 15 min showed no decrease in mechanical hyperalgesia. As shown in

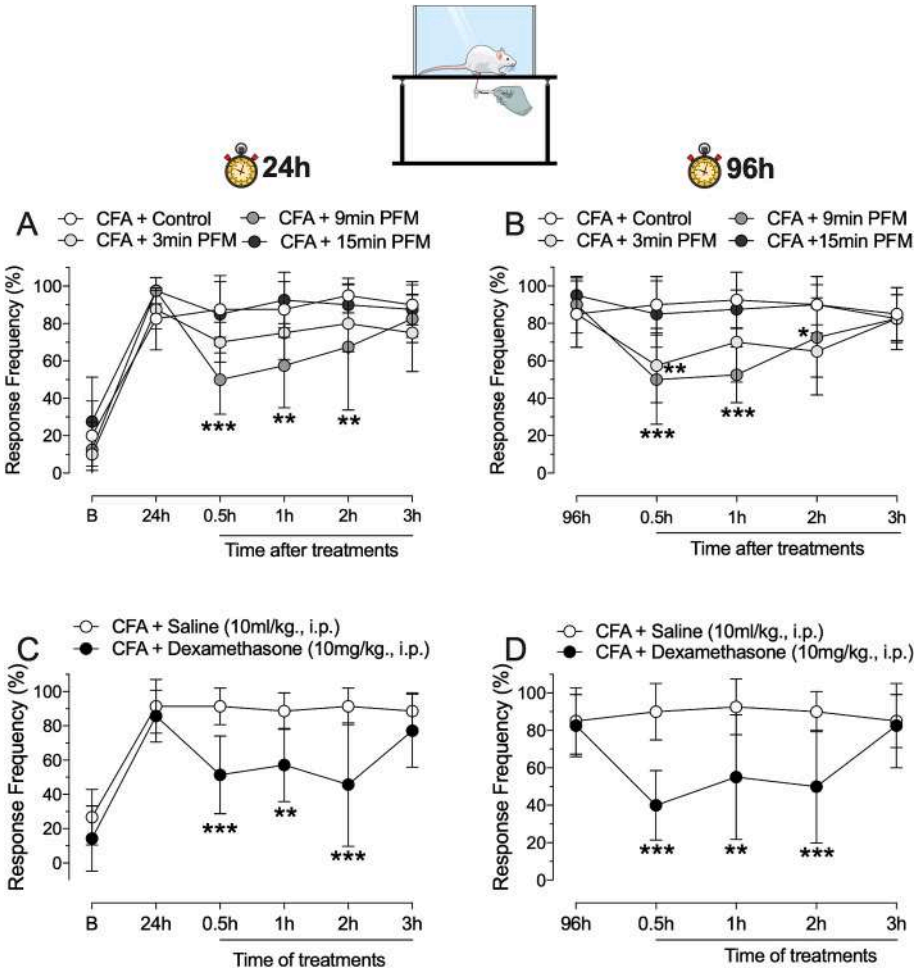

Fig. 2. Antihyperalgesic effect of PFM and dexamethasone on mechanical hyperalgesia induced by CFA paw injection. Time-course effect on day 1 (panels A and B, respectively). Time-course effect on day 5 (panels C and D, respectively). Each dot represents the average of 8 animals, and the vertical lines show the standard deviation. performed by two-way ANOVA followed by the Bonferroni post hoc test. $^{*}P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$ when compared with control group. PFM, plantar fascia manipulation; CFA, Complete Freund's Adjuvant; h, hours.

Fig. 2B, at 96 h after CFA, mechanical hyperalgesia was reduced in the PFM 3 min and PFM 9 min groups for up to 30 min ($P = 0.0014$ and $P = 0.0001$, respectively) after the end of the treatment. However, this effect lasted up to 2 h ($P = 0.0220$) in the PFM 9 min group.

As depicted in Fig. 2 C-D, dexamethasone treatment produced significant antihyperalgesia on 24 h (30 min $P = 0.011$ for up 2 h, $P = 0.0001$) and 96 h (30 min $P = 0.0001$ for up 2 h, $P = 0.0005$) after CFA.

The impact of different PFM treatment times on paw edema

Figs. 3A-B shows that acute treatment at 24 and 96 h with PFM at different times (3 min, 9 min, or 15 min) was not able ($P>0.05$) to reduce paw edema. Furthermore, treatment with dexamethasone (positive control) reduced ($P = 0.001$) edema only twenty-four hours after CFA. However, the greatest reductions in edema were observed 24 h in the dexamethasone (maximal inhibition – MI: –23 ± 3 %) and PFM 9 min (MI: −10 ± 3 %) groups. 96 h after CFA, the PFM 3 min group presented MI: −6 ± 4 %).

Effects of caffeine administration through peripheral and central sites on antihyperalgesic action of PFM

Firstly, we determined the effect of caffeine, a non-selective antagonist of adenosinergic receptors, on antihyperalgesic action of PFM; we then evaluated the influence of caffeine pretreatment by different routes in both 24 and 96 h (Fig. 4A and F). At 24 h after CFA i.pl. injection, two-way RM ANOVA revealed significant main effects of i.p. caffeine pretreatment [$F(1, 25) = 9.871$; $P = 0.0043$] and PFM treatment [$F(1, 25) = 5.971$; $P = 0.0219$] and i.p. caffeine pretreatment x PFM treatment interaction [$F(1, 25) = 7.930$; $P = 0.0094$]. The systemic administration of caffeine (20 min before) prevented ($P = 0.0018$) the antihyperalgesic effect of PFM. This effect was also observed when caffeine was administered to the animals by the i.pl. or i.t. routes. Thus, two-way RM ANOVA revealed significant main effects of i.pl. caffeine pretreatment [$F(1, 28) = 6.918$; $P = 0.0137$] and PFM treatment [$F(1, 28) = 14.78$; $P < 0.0006$] and i.pl. caffeine pretreatment x PFM treatment interaction [$F(1, 28) = 9.211$; $P = 0.0052$]. To i.t. caffeine pretreatment two-way RM ANOVA also revealed significant main effects of i.t. caffeine pretreatment [$F(1, 28) = 9.942$; $P = 0.0038$] and PFM treatment [$F(1, 28) = 16,43$; $P < 0.0004$] and i.t. caffeine pretreatment x PFM treatment interaction [$F(1, 28) = 20.29$; $P = 0.0001$].

At 96 h after CFA i.pl. injection, two-way RM ANOVA revealed significant main effects of i.p. caffeine pretreatment [$F(1, 24) = 6.153$; $P < 0.0205$] and i.p. caffeine pretreatment x PFM treatment interaction [$F(1, 24) = 11.44$; $P = 0.0025$], but did not of PFM treatment [$F(1, 24) = 4.119$; $P = 0.0536$]. The systemic administration of caffeine (20 min before) prevented ($P = 0.0022$) the antihyperalgesic effect of PFM. This effect was also observed when caffeine was administered to the animals by the i.pl. or i.t. routes. Thus, two-way RM ANOVA revealed significant main effects of i.pl. caffeine pretreatment [$F(1, 28) = 8.702$; $P =$

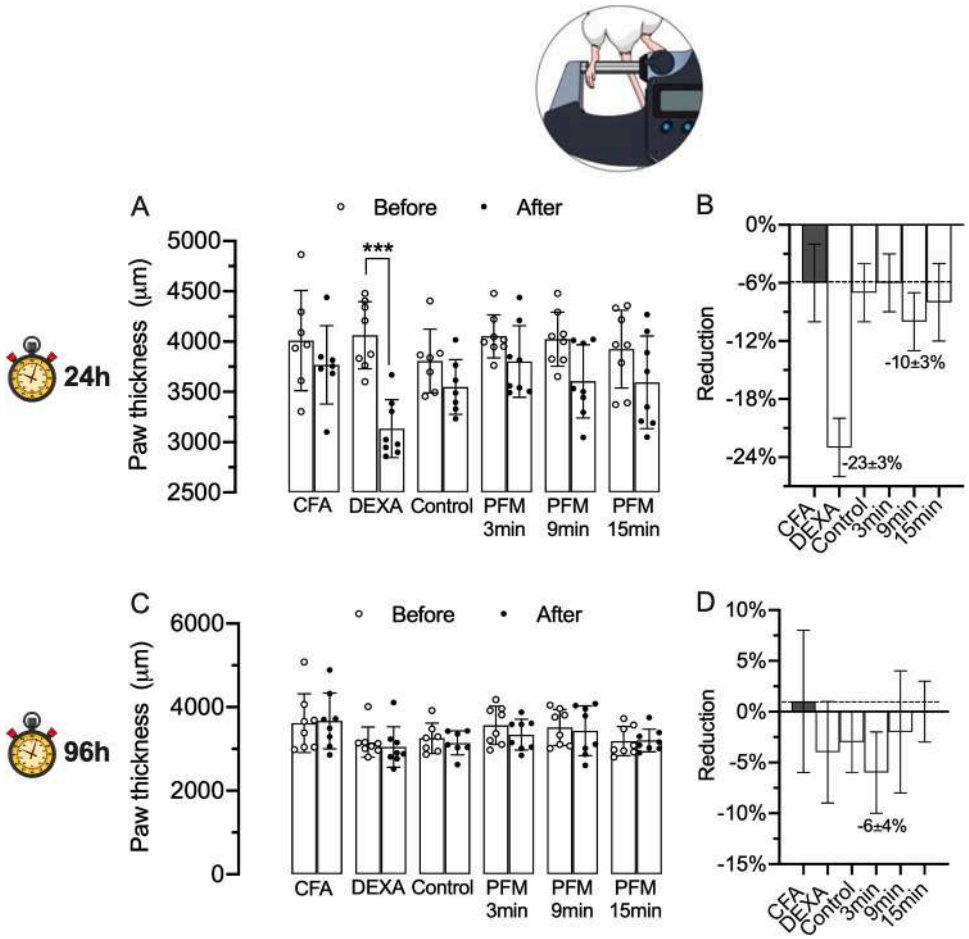

Fig. 3. Effect of PFM on paw edema. Results expressed as the difference between the thickness of the right hind paw and the baseline value of the same paw (panels A and C). Results expressed as the difference of thickness of the right hind paw before and after treatment (panels B and D). Bars represent the average of 8 animals, and the vertical lines show the standard deviation of the mean. Performed by two-way ANOVA followed by the Bonferroni post hoc test. *$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$ when compared with control group. PFM, plantar fascia manipulation; CFA, Complete Freund's Adjuvant, DEXA, dexamethasone; min, minutes.

0.0064] and PFM treatment [F (1, 28) = 6.536; $P = 0.0163$] and i.pl. caffeine pretreatment x PFM treatment interaction [F (1, 28) = 4.680; $P = 0.0392$]. To i.t. caffeine pretreatment two-way RM ANOVA also revealed significant main effects of i.t. caffeine pretreatment [F (1, 28) = 9.871; $P = 0.0044$] and PFM treatment [F (1, 28) = 9.873; $P = 0.0049$] and i.t. caffeine pretreatment x PFM treatment interaction [F (1, 28) = 9.877; $P = 0.0051$].

The percentage of response frequency values for the group i.p., i.pl. or i.t. treated with caffeine was significantly higher when compared with the respective control group (treated with saline plus PFM for 9 min, 30 min after treatments, Fig. 4A-F). However, caffeine (i.p., i.pl. or i.t.) alone did not promote modifications to the animal's frequency of paw withdrawal response.

Evaluation of peripheral and central A_1Rs' role on antihyperalgesic action of PFM

To verify whether the antihyperalgesic effect of PFM can be mediated via the activation of A_1R, we administrated the selective A_1R antagonist, DPCPX, in different sites. At 24 h after CFA i.pl. injection, two-way RM ANOVA revealed significant main effects of i.pl. DPCPX pretreatment [F (1, 28) = 13.76; $P = 0.0009$] and PFM treatment [F (1, 28) = 21.00; $P = 0.0001$] and i.pl. DPCPX pretreatment x PFM treatment interaction [F (1, 28) = 13.76; $P = 0.0009$]. The i.pl. administration of DPCPX (15 min before) prevented ($P = 0.0001$) the antihyperalgesic effect of PFM. This effect was also observed when caffeine was administered to the animals by the i.t. route. Thus, two-way RM ANOVA revealed significant main effects of i.t. DPCPX pretreatment [F (1, 28) = 32.71; $P = 0.0813$] and PFM treatment [F (1, 28) = 83.74; $P = 0.0073$] and i.t. DPCPX pretreatment x PFM treatment interaction [F (1, 28) = 10.60; $P = 0.0030$].

At 96 h after CFA i.pl. injection, two-way RM ANOVA revealed significant main effects of i.pl. DPCPX pretreatment [F (1, 27) = 9.041; $P = 0.0057$] and PFM treatment [F (1, 27) = 9.051; $P = 0.0051$] and i.pl. DPCPX pretreatment x PFM treatment interaction [F (1, 27) = 9.045; $P = 0.0053$]. The i.pl. administration of DPCX (15 min before) prevented ($P = 0.0016$) the antihyperalgesic effect of PFM. This effect was also observed when caffeine was administered to the animals by i.t. route. Two-way RM ANOVA revealed significant main effects of i.t. DPCPX pretreatment [F (1, 24) = 16.73; $P = 0.0004$] and PFM treatment [F (1, 24) = 10.02; $P = 0.0042$] and i.t. DPCPX pretreatment x PFM treatment interaction [F (1, 24) = 10.05; $P = 0.0042$].

The percentage of response frequency values for the groups pretreated with DPCPX via i.pl. or i.t. routes were significantly higher when compared to DMSO+PFM 9 min group; this was shown for 30 min after PFM in both 24 and 96 h (Fig. 5A-D). DPCPX without PFM had no effect on response frequency. Spinal and intraplantar administration of DPCPX, 15 min before PFM 9 min, prevented the decrease of the response frequency resulting from the treatment ($P = 0.01$) in both 24 and 96 h (Fig. 5A-D). These findings suggest that central and peripheral activation of A_1R mediates the antihyperalgesic effect of PFM 9 min in the CFA pain model.

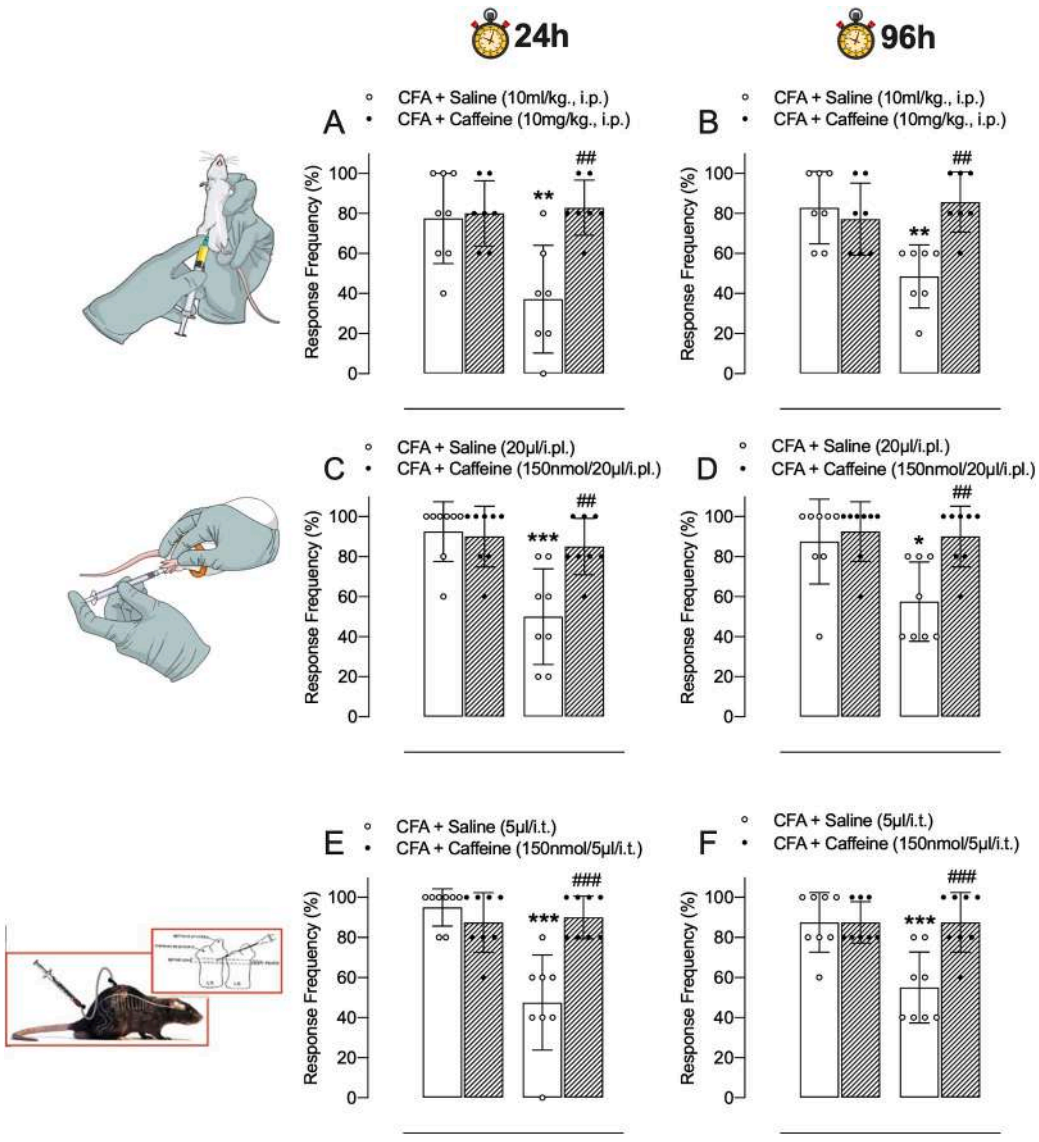

Fig. 4. Intraperitoneal (panels A and B), intrathecal (panels C and D), and intraplantar (panels E and F) pretreatment with caffeine and the antihyperalgesic effect of 9 min of plantar fascia manipulation (PFM) in mice. White bars show the CFA (control) + saline group or the antihyperalgesic effect of 9 min of PFM. Dark bars show the effects of caffeine (10 mg/kg, i.p.; 150 nmol/site, i.t.; or 150 nmol/paw, i.pl.) antagonist injected before 9 min of PFM treatment. Each point represents the mean of 8 animals, and vertical lines show the standard deviation of the mean. $^{*}P < 0.05$ or $^{***}P < 0.001$ when compared with CFA+saline + control groups or ### when compared with CFA+saline + 9 min of PFM groups. PFM, plantar fascia manipulation; CFA, Complete Freund's Adjuvant, i.p., intraperitoneal; i.t., intrathecal; i.pl., intraplantar.

Discussion

The present study demonstrates that PFM performed by the Myofascial Reorganization® technique, a MF approach, elicits a time-dependent reduction of the CFA-induced hyperalgesia mechanical response in mice. The most relevant additional findings of the present work are that (i) the antihyperalgesic action of PFM against CFA-induced hyperalgesia mechanical response was significantly prevented by i.p., i.pl. and i.t. treatments of animals with caffeine; (ii) central (spinal) and peripheral (paw) administration of DPCPX also prevented the decrease in the response frequency resulting from the treatment with PFM in both 24 and 96 h after CFA. These findings suggest that central and peripheral activation of A_1R mediates the antihyperalgesic effect of PFM in the inflammatory pain model.

In the present study, our results showed that twenty-four hours after CFA injection, only the acute PFM 9 min treatment produced antihyperalgesic effects for up to 2 h after treatment. Furthermore, in the evaluation at 96 h after CFA injection, the groups treated with PFM 9 min and PFM 3 min, but not PFM 15 min, also showed an antihyperalgesic effect for up to 2 h after the treatments. Here, we use only females because many persistent inflammatory pain conditions occur in women who have had unsuccessful treatment. Furthermore, the neuroendocrine difference between the sexes is well established, a fact that encourages studies that analyze therapeutic possibilities for controlling inflammatory pain in females. We have previously found fundamental differences in endogenous pain control mechanisms between males and females (De Oliveira et al., 2021). At least to our knowledge, this is the first time in the literature that the analgesic effect of PFM has been demonstrated in a preclinical study. Thus, due to this originality of our study, direct comparison with other studies is not possible. In this sense, the discussion was conducted comparing the results obtained with similar manual therapy techniques, such as AJM, which during its execution has a component of PFM (Martins et al., 2012; Martins et al., 2013; Martins et al., 2011; Salgado et al., 2019). In this sense, the reduction of mechanical hyperalgesia after AJM has been demonstrated in animal models for almost two decades (Martins et al.,

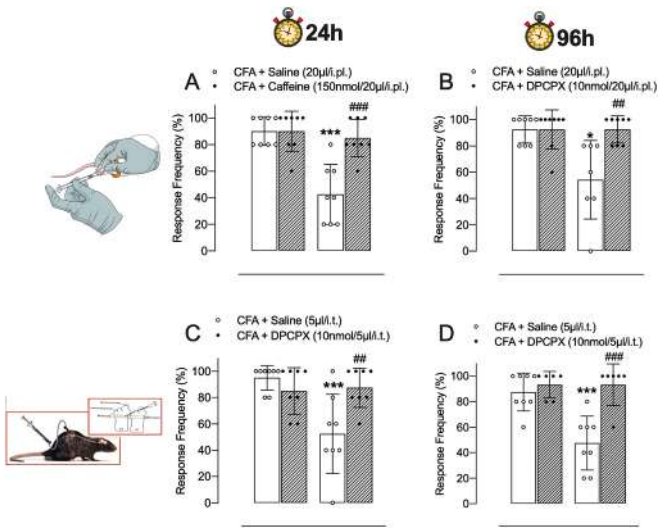

Fig. 5. Depicted are the intraplantar (panels A and B) and intrathecal (panels C and D) pretreatments with DPCPX and the antihyperalgesic effect of 9 min of plantar fascia manipulation (PFM) in mice. White bars show the CFA (control) + saline group or the antihyperalgesic effect of 9 min of PFM. Dark bars show the effects of DPCPX (10 nmol/site, i.pl.; or 10 nmol/site, i.t.) antagonist injected before 9 min of PFM treatment. Each point represents the mean of 8 animals, and vertical lines show the standard deviation of the mean. $^{**}P < 0.01$ or $^{***}P < 0.001$ when compared with CFA+saline + control groups or $\#\# P < 0.01$ or $\#\#\# P < 0.001$ when compared with CFA+saline + 9 min of PFM groups. PFM, plantar fascia manipulation; CFA, Complete Freund's Adjuvant; DMSO, Dimethyl sulfoxide; DPCPX, N6-[2-(3,5 dimethoxyphenyl) 2(methyl-phenyl)ethyl] adenosine; i.p, intraperitoneal; i.t., intrathecal i.pl., intraplantar.

2012; Martins et al., 2013; Martins et al., 2013; Martins et al., 2011; Salgado et al., 2019; Sluka and Wright, 2001). Omura *et al.* (Omura et al., 2022) showed that AJM 9 min, similar to PFM 9 min, also reduced mechanical hyperalgesia at 24 and 96 h after CFA injection. Using an animal model of postoperative pain, which is also a model of nociceptive pain like the one in the present study, they also found that AJM reduced mechanical hyperalgesia when performed for 9 min, but not for 3 min in animals with postoperative pain. Thus, our results confirm and extend the literature data by demonstrating that PFM reduced mechanical hyperalgesia-induced pain, of inflammatory origin, in a time-dependent manner (França et al., 2020; Martins et al., 2013; Martins et al., 2013; Omura et al., 2022).

In this study we used the well-established CFA-induced peripheral inflammatory nociceptive pain model, which allows the quantification of mediators involved in cellular changes during the inflammatory process (Martins et al., 2015; Trento et al., 2021). In addition, i.pl. of CFA triggers persistent hyperalgesia that can be easily assessed by behavioral von Frey filament (vF) test. Our research group has used the CFA model routinely, evaluating mechanical hyperalgesia generally at different time lengths, such as twenty-four and ninety-six hours after CFA injection (Vieira et al., 2021). This approach is due to the predominance of different cell types found throughout each phase of inflammation. In the early phase of inflammation, neutrophils are the predominant leukocyte population, while during the late phase, macrophages are more prevalent (Brack et al., 2004). Several studies have performed behavioral tests 24 h after CFA injection, defining it as an early phase of inflammation, and 96 h after CFA injection, defining it as a late phase of inflammation. Several endogenous mediators are responsible for pain control, such as opioids (met-enkephalin and β-endorphin), which are produced and released from neutrophils and monocytes/macrophages (Rittner et al., 2001; Rittner et al., 2009; Rittner et al., 2006). Thus, the evaluation of mechanical hyperalgesia in the two phases of inflammation can facilitate the investigation of the PFM mechanism of action relative to the cellular profile of the local inflammation model. In the present study, we found that in the early phase of inflammation only PFM 9 min had an antihyperalgesic effect, while in the late phase of inflammation the treatment with a shorter time (PFM 3 min) also had an effect. This may support the idea that PFM action more effectively depends on late inflammatory cells such as macrophages. However, future studies that analyze the cell profile with histological experiments or with cytometry are necessary to corroborate this statement.

Despite the observed antihyperalgesic effect, acute treatment with PFM failed to reduce paw edema. In addition, dexamethasone (used as a positive control) was effective in reducing edema in the early, but not in the late phase of inflammation. These results suggest that the action of PFM may be partly analgesic and not very anti-inflammatory. This result is strengthened by the findings of Omura et al. (Omura et al., 2022), who did not observe a decrease in interleukin −1 and tumor necrosis factor (pro-inflammatory cytokines) in the inflamed paw (CFA) of mice treated with AJM 9 min.

It has been speculated that non-allopathic treatments of pain, such as chiropractic manipulations and massage, and modalities that involve the mechanical manipulation of joints and muscles, might also be associated with an efflux of cytosolic ATP that is sufficient to elevate extracellular adenosine (Goldman et al., 2010). We have previously demonstrated that AJM-induced analgesia, a MT technique involving direct mechanical manipulation of joints and indirect muscle manipulation, was prevented by caffeine or DPCPX, a selective antagonist for A_1R. Our findings confirm and extend the hypothesis that mechanical manipulation of joints and muscles might also be associated with the availability of adenosine, and that peripheral (paw) administration of caffeine or DPCPX before PFM nullified the treatment's decrease in the withdrawal response frequency. These findings suggest that peripheral activation of A_1Rs contributes to the antihyperalgesic effect of PFM on inflammatory pain. The musculoskeletal system is entirely involved by fascial tissue, which is primarily composed of fibroblasts (Fede et al., 2021). The hypothesis about the involvement of the adenosinergic system in analgesia induced by mechanical fibroblast stimulation has been raised for more than a decade and has been developed through acupuncture studies (Burnstock, 2009; Goldman et al., 2010; Langevin, 2014). Initially, rotation of needles inserted into myofascial tissue was shown to cause it to stick to loose connective tissue at the areola, producing mechanical stimulation of the fibroblast causing analgesia (Langevin et al., 2001; Langevin et al., 2002; Langevin and Yandow, 2002). This was supported by the fact that injecting collagenase into the tissue surrounding the needle diminished this immediate analgesic effect in rats (Yu et al., 2009). In this sense, it has also been shown that mechanical force is capable of altering the morphology and viscoelastic properties of the fibroblast, which reflects on the rigidity and viscosity of the entire areolar connective tissue (Langevin et al., 2005; Langevin et al., 2011). Ex vivo tissue stretching caused a time-dependent increase in fibroblast cell body perimeter and cross-sectional area. At 2 h, the mean cross-sectional area of the fibroblast cell body was 201 % greater in elongated tissue than in non-stretched tissue (Langevin et al., 2005). Finally, gentle, static stretching of connective tissue for 10 min has been shown to have an antifibrotic effect (Bouffard et al., 2008). Thus, this evidence supports the influence of PFM on fibroblast function. It is believed that this analgesia depends on mechanical stimulation of the fibroblast by either acupuncture or manual therapy, resulting from the interaction of adenosine (released by the fibroblasts) activating A_1R, which is expressed in peripheral nociceptive neurons (Goldman et al., 2010; Langevin, 2014).

It has been shown that adenosine, in the central nervous system is an important neuromodulator and that it regulates neuronal and non-neuronal cell function (eg. microglia) through actions on extracellular adenosine receptors. In the spinal cord, adenosine also regulates pain transmission, therefore various therapies that can alter the extracellular availability of adenosine may modulate pain transmission, particularly by activating adenosine A_1R (Sawynok, 1998; Sawynok and Liu, 2003).

Thus, the activation of spinal A_1Rs produces antinociception in the model of inflammatory pain (Madeira et al., 2021). In the present study it was also shown that i.t. of caffeine or DPCPX also prevented the antihyperalgesic effect of PFM in mice with paw inflammation. These results suggest that the antihyperalgesic effect of PFM seems to be mediated, at least in part, by spinal A_1R. These findings may be related to the sensory afferents found in PF. PF contains several free nerve endings and Pacini and Ruffini corpuscles (Stecco et al., 2013) that are present in Aβ low-threshold mechanoreceptors, which are the main type of primary sensory neurons that mediate discriminative touch and tactile perception in mammals (Fleming and Luo, 2013). According to their rates of adaptation to sustained mechanical stimuli, low-threshold Aβ mechanoreceptors are classified as either rapidly adapting or slowly adapting (Iggo, 1984; Mountcastle, 1957) Pacinian (Iggo, 1984) and Ruffini corpuscles (Paré et al., 2003), respectively. Aβ low-threshold mechanoreceptors enter the spinal cord and send short branches to the substantia gelatinosa, and long central branches directly to the dorsal column nuclei and to the cerebral cortex, thus participating in pain control (Melzack, 1999; Melzack, 2005). This evidence provides neurophysiological support to hypothesize that PFM can influence spinal neurotransmission through A_1R activation.

In summary, the results of this study largely extended previous data by demonstrating that PFM decreased CFA-induced mechanical hyperalgesia and that this effect was prevented by the pretreatment of caffeine given via intraperitoneal, intrathecal, and intraplantar routes. We also showed that intrathecal and intraplantar administrations of DPCPX blocked the antihyperalgesic effect of PFM. To our knowledge, this is the first direct demonstration of the role of the A_1R in mediating the antihyperalgesic effect of PFM. Additionally, we suggest assessing A_1R via biochemical analysis to determine if PFM increases the adenosine levels. The lack of biochemical analysis may be a limitation of this study and should be considered in future studies.

Ethics approval

Were approved by the Ethics Commission for the Use of Animals of University of Southern Santa Catarina (CEUA-Unisul) (protocol number 21.021.4.01.IV, approved on 13/09/2021).

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CRediT authorship contribution statement

Maria Eugenia Ortiz: Methodology, Data curation, Conceptualization. **Larissa Sinhorim:** Methodology, Data curation, Conceptualization. **Bruna Hoffmann de Oliveira:** Writing – review & editing, Methodology, Data curation. **Rafaela Hardt da Silva:** Writing – review & editing, Methodology, Data curation. **Gabriel Melo de Souza:** Writing – review & editing, Methodology, Data curation. **Gabriela de Souza:** Writing – review & editing, Methodology, Data curation. **Anna Paula Piovezan:** Writing – review & editing, Methodology, Conceptualization. **Edsel Balduino Bittencourt:** Writing – review & editing, Methodology, Data curation. **Gianluca Bianco:** Writing – review & editing, Methodology, Data curation. **Afonso Shiguemi Inoue Salgado:** Writing – review & editing, Methodology, Data curation. **Werner Klingler:** Writing – review & editing, Methodology, Data curation. **Robert Schleip:** Writing – review & editing, Methodology, Data curation. **Daniel Fernandes Martins:** Conceptualization, Supervision, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Effect of myofascial release techniques on internal biomechanics and their resultant application to sports: A systematic review

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ABSTRACT

Objective: To investigate the influence of myofascial release (MFR) techniques on biomechanical parameters, including force, speed, Range of Motion (ROM), and flexibility in athletes.
Method: This is a systematic review conducted on the databases United States National Library of Medicine (PubMed), Scopus, Scientific Electronic Library Online (SciELO); LILACS, and Embase. The PRISMA guidelines – 2020 were followed, and bias risk analysis was performed using the Cochrane Handbook tool (RoB2).
Results: Sixteen studies were included for qualitative analysis. Techniques using MFR applied or self-applied to improve strength, speed, ROM and flexibility, have no consensus regarding the period of their applicability, due to difficulties in identifying the ideal load of applied tension, temperature level, and viscoelastic properties during the release of the deep fascia. However, improvements in oxygenation, reorganization of piezoelectricity, and normalization of fascial tension became evident after MFR.
Conclusion: Regarding strength, speed, and range of motion (ROM), instrument-assisted soft tissue mobilization performed in isolation and self-applied techniques combined with other methods emerged as favorable predictors for lower limb outcomes. However, isolated self-myofascial release requires further investigation. Regarding flexibility, there is a contrast in results between the use of self-applied foam rolling in isolation, which seems to prevent densification but suggests improvements in muscle strength acquisition without compromising flexibility. Applied MRF provided a more flexible quality for scapular mobilization, both in isolation and in combination with other techniques, but its best indication and/or specific applicability is for pain reduction.

1. Introduction

Fascia is defined as a structure that contains loose (areolar) and dense connective tissue (Dawidowicz et al., 2016). In its composition, it presents collagen in the basal portion and extracellular matrix with the possibility of presenting components of adipose tissue (Dawidowicz et al., 2016; Adstrum et al., 2016; Pirri et al., 2021; Fede et al., 2022). Among the four fascias contained in the human body, the deep fascia known as muscular fascia (MF) is divided into aponeurotic and epimysial, rich in collagen fibers and constituted by a tensional chain that involves different structures, which are called the fascial system (FS) (Fede et al., 2021).

This morphological structure establishes a collaborative work among connective tissues, instituting a dynamic of movement and functionality within the muscular system (Schleip et al., 2019; Fede et al., 2021). So far, the literature findings on the FS have revealed conceptions related to its functional properties, containing rigid and elastic elements, and a capacity to shape joints and muscles through a cellular process that converts mechanical stimuli into chemical responses (França et al., 2020). With regard to the MF, its functional integration capacity is already evident in the scientific literature, which enables a transfer of force that interferes with internal biomechanics, the latter being the physical and biological aspects of joints, bones and histological tissues, mainly considering muscle tissue (Adstrum et al., 2016; Fede et al., 2021). This mechanism is manifested through a composition formed by receptors in fibroblasts, synoviocyte cells, and myofibroblasts contained in the fascial structure (Adstrum et al., 2016; Schleip et al., 2019). It is worth highlighting the reorganization of energy, i.e. the piezoelectricity

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established by the MF, which can be restructured when it is in adhesion (Beardsley and Škarabot, 2015).

However, MF requires special conditions to effect different tensions and, primarily, the sensory properties that can propagate through its structural composition. Therefore, techniques to release and/or reorganize the MF suggest further investigation and analysis of its possibilities, even with the identification of limited satisfactory results already evident in scientific findings. Myofascial release (MFR) seems to signal clinical relevance not only in reorganization from tissue adjustment but also in dynamic changes in fluids in an oxygenation process that propels itself upward (Sinhorim et al., 2019).

In the conditions inherent to sports, athletes seek manual therapies with the purpose of improving sports performance (França et al., 2023). However, myofascial adhesions are suggested to be a complication that hinders this process, as both the increase in intramuscular pressure and the mechanical compression of blood vessels predispose to its fatigue through the occurrence of aerobic inefficiency due to decreased oxygenation (Amorrim et al., 2022). The human body seeks to capture the highest rate of oxygen during intense exercise, with maximal oxygen consumption (VO2max) being a parameter to distinguish between trained and untrained subjects (Bassett and Howley, 2000; Faude et al., 2009).

The MFR is divided into two categories: the MFR technique applied by a therapist, and the MFR technique self-applied by the individual. The main techniques using MFR (applied) can be with the use of the hands or through instrumental myofascial release (IMR), also known as instrument-assisted soft tissue mobilization (IASTM), using cups, scrapers, needles, or hooks. The second category (self-applied) is called self-myofascial release (SMR), developed through a self-applied release with foam rolling (FRSMR). For this maneuver, the individual lies down or supports the appendicular limbs on a foam roller (Wiewelhove et al., 2019).

These strategies appear to be an opportunity to transcend from motivational effects to their clinical applications and feasible improvements in athletes' performance. Among others, for the gain in height and power in a countermovement jump (CMJ), range of motion (ROM), flexibility, speed, and strength (França et al., 2023). Thus, the athlete's preparation needs a more specific investigation, since the strategy with FRSMR improved the athletes' ROM compared to the MFR applied by a therapist (Cheatham et al., 2015). However, both the use of IMR and FRSMR are still questionable in terms of their applicability to the biomechanical characteristics and particularities of the myofascial system.

Investigating the strength derived from MFR, considering the type of technique, the timing of its applications, and the factors that may hinder athletes' adaptations to innovative strategies, can fill gaps and enhance contemporary protocols. Thus, the aim of this study was to verify the influence of MFR techniques on internal biomechanical parameters considering the strength, speed, ROM, and flexibility of athletes.

2. Methods

A systematic review was conducted, following the methodological guidelines of PRISMA-2020 (Page et al., 2021). The protocol for this systematic review was registered in CRD 42024501254 (Centre for Reviews and Dissemination) in the international prospective register of systematic reviews (PROSPERO).

2.1. Eligibility criteria

Inclusion criteria: intervention studies involving healthy individuals of both genders, aged 11 years and older, practicing some form of physical exercise who received MFR interventions and techniques. Only studies published in the last 10 years were considered for qualitative synthesis. Topics of interest: biomechanical aspects and sports performance following the use of myofascial release strategies. For qualitative analysis, randomized controlled trials (RCT) and randomized crossover clinical trials (RCCT) were advocated. Review studies, observational studies, books, and laboratory research were not included in the qualitative analysis but could be included only in cases of relevance to enrich through specific information. The same procedure was adopted regarding methodological studies containing literature search strategies and methods for the development of review studies.

Exclusion criteria: Studies were excluded if they did not address aspects related to MFR techniques; involved a different population; did not elucidate methods and results regarding strategies and factors related to sports performance. Similarly, studies of personal opinions, observational and laboratory studies, editorials, comments, letters, brochures, newspapers, and conference abstracts were not considered for this research.

2.2. Sources of information

The following databases were used: Scopus, PubMed/MEDLINE, Latin American and Caribbean Health Sciences Literature (LILACS), SciELO, and Embase. The reference lists of included studies were manually analyzed to assess the importance of including additional references. The search was conducted using the Health Science Descriptors (DeCS) from the Virtual Health Library Lilacs for obtaining specific keywords.

2.3. Search strategies

The search for descriptors was conducted on October 25, 2023, and the search for scientific studies was carried out between November 29, 2023, and December 11, 2023. The following descriptors were selected: Musculoskeletal manipulations, Performance, Fascia, Physical activity, associated with the boolean operators "AND" and "OR". The distribution occurred as follows:

Scopus ((musculoskeletal AND manipulation) AND (fascia) OR (performance) AND (physical AND activity); (performance) AND (physical AND activity) OR (musculoskeletal AND manipulation) AND (fascia)). SciELO: ((Musculoskeletal manipulation) OR (Fascia) OR (Performance) AND (physical activity)); (Fascia) OR (Performance) OR (physical activity) OR (Musculoskeletal manipulations)). PubMed/MEDLINE: ((Performance) OR (physical activity) OR (Musculoskeletal manipulations) OR (Fascia)); ((physical activity) OR (Musculoskeletal manipulations) OR (Fascia) OR (Performance)). LILACS *((Performance) OR (physical activity) OR (Musculoskeletal manipulations) AND ((Fascia) OR (Performance) OR (physical activity) OR (Musculoskeletal manipulations)). Embase: ((physical activity)) AND (Musculoskeletal manipulations) OR (Fascia) OR (Performance)); ((Performance) AND (physical activity) OR (Musculoskeletal manipulations) AND (Fascia))*.

The search for eligible studies was assisted by the PICO strategy (Santos et al., 2007), mediated by the question: "What is the influence of MFR techniques on biomechanical parameters, considering the force, velocity, ROM, and flexibility of athletes?" Thus, for the population of interest, individuals practicing physical exercise from 11 years of age and older were included. As for the intervention, it consisted of connective tissue mobilization techniques with MFR techniques. In the comparison, studies with a placebo or control group were included. In the outcome, the search focused on different outcomes containing statistical, systematic, absolute, and relative data of tests for physical fitness, strength, power, flexibility, stiffness, ROM, and pain relief. It was decided to develop a table with the general characteristics of the studies containing the following items: author, year of publication, study type, country, sport modality, sample size, gender, control group, experimental group, inclusion and exclusion criteria, total treatment period, and evaluated outcome. The results of the techniques and systematic values were part of the discussion.

2.4. Selection process

A protocol with pre-established criteria was developed, and although there was a limitation on the inclusion year, the guidelines prioritized the most recent studies with the strongest scientific evidence. The internal validity of the research was emphasized, and the information was supported by the guidelines of the Centre for Evidence-Based Medicine, Oxford, UK, which is akin to the pyramid guidelines (Murad et al., 2016).

2.5. Data collection and listing process

The search results from the databases were stored in a bibliographic reference management software, EndNote X9.1 (Clarivate Analytics).

The reading of titles, abstracts, and analysis of results was conducted by two researchers, who analyzed and extracted data from the selected articles using a standardized form, according to eligibility criteria, through several stages. In the first stage, two reviewers assessed each title. The second stage involved screening the abstracts of the studies included in the first stage. In the third stage, the studies underwent full-text screening. Studies that met the inclusion criteria were selected by both reviewers and included in the systematic review, as shown in Fig. 1. In case of disagreement between reviewers, a third reviewer conducted a priority check.

The following information was extracted: 1) characteristics of the included studies; 2) characteristics of the participants; 3) description of the variables and instruments used; 4) intervention performed; 5) intervention time; 6) main results. The research should contain the types of techniques and methods used by the researchers and neurophysiological aspects. As for the outcomes, they should contain elucidated systematic data on the effect size in sports performance after MFR techniques. In the organization of Table 1, two authors collected information in the selected studies, considering the author and year of publication, data collection location, study type, number of participants, sample size, treatment period, and factors in the applicability of self-myofascial release. Simultaneously, aspects of flexibility, pain, ROM, and stiffness were verified. (Table 1). Subsequently, the collected data were checked, and a third author would decide. Following that, a fourth author verified possible divergences and the way they were inserted into the table. Consequently, the articles were subjected to bibliometric analysis by the reviewers using the bibliometric software Sitkis. The purpose of this co-citation analysis of keywords was to evaluate the frequency and interaction of the descriptors present in the selected studies (Schildt, 2002). Thus, the analysis of keywords would allow a retrospective evaluation of the quality of the article selection process used, as shown in Fig. 2.

For discussion, the selected studies were reorganized into topics, with the inclusion of three themes strongly related to the main objective of the present research: 1) Characteristics in the constitution of the fascia and particularities from MF; 2) Types of MFR applied by a therapist and

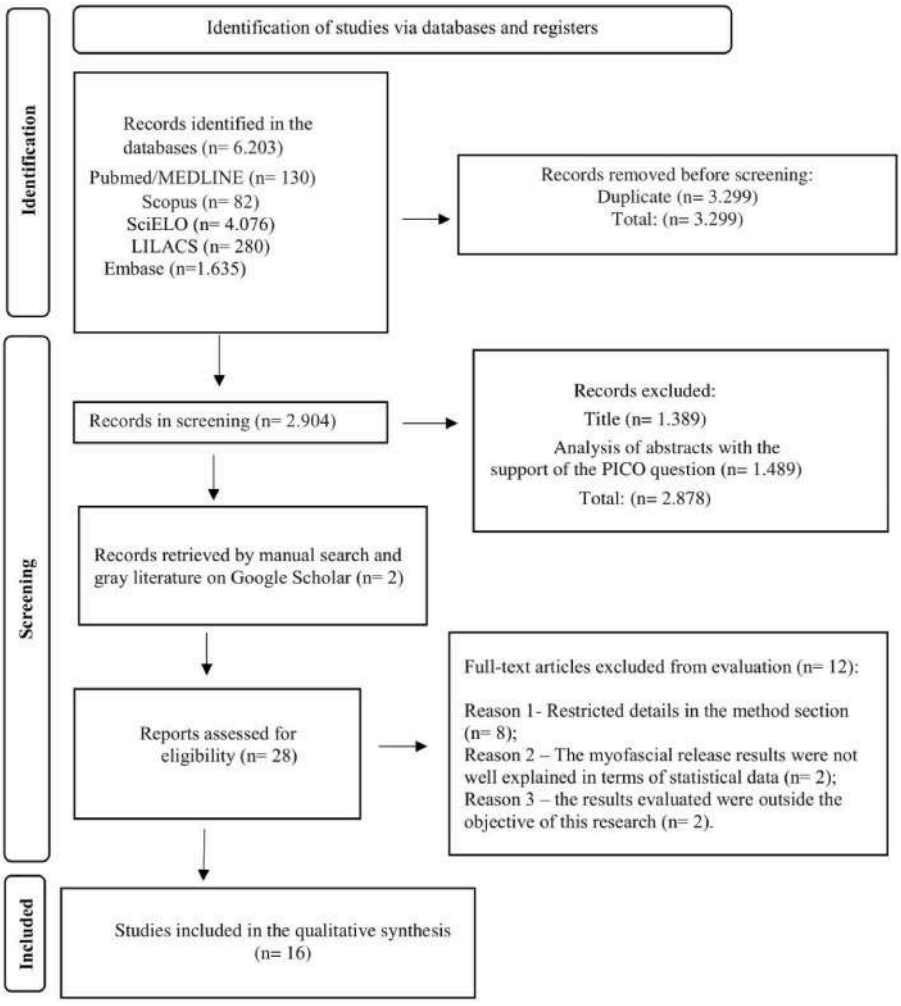

Fig. 1. - Flowchart of the selection process for the literature search. Florianópolis, SC, Brazil, 2023.
Source: Checklist de Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD et al. PRISMA statement 2020: uma diretriz atualizada para relatar revisões sistemáticas. BMJ 2021; 372:71. https://doi.org/10.1136/bmj. n71. For more information, visit: http://www.prisma-statement.org/.

Table 1
- General characteristics of the studies included in the qualitative synthesis.

Author/Year/Study Type/ Country	Sport/n/MA/Gender	CG/EG/CI/CE	Total intervention period/Evaluated outcome
Afanador-Restrepo et al. (2023)/(RCES)/(Colombia)	Volleyball, basketball and soccer/(n = 87)/MA (20,5 ± 2,3)/M. F.	EG ((ROM + FR) (n = 43))/CG (FR) (n = 44)/IC (≥18 years old, being active in one of the collective sports programs of the Andean University Foundation, without musculoskeletal issues, injury, or pain)/EC (MMII injury)	Period 8 weeks, 2 times a week/ROM, VJ, increase of strength and flexibility (low back muscles and Hamstring)
Behara and Jacobson (2017)/(RCCT)/(USA)	Soccer/(n = 14) MI (20 ± 1,4)/M.	EG ((FR (n = 14))/CG ((DS (n = 14))/IC (no injury to the MMII, disease that could affect strength, power, flexibility/ EC (Not reported)	Total 8min MMII/Strength, power, flexibility, CMJ (Hamstring and quadriceps).
Bond et al. (2019)/(RCES)/(Japan)	Bodybuilding (n = 20)/ MA: (39,9 ± 8,7)/F.	EG (n = 10)/CG (n = 10)/IC (non-muscle trainers, no injuries)/EC (Not reported)	Period 10 weeks/Increase of strength (Pectoral muscles, gluteus, Hamstring and Quadriceps)
Blades et al. (2022)/(RCES)/(United Kingdom)	Boxing/(n = 11)/MA (22 ± 2)/M.	EG ((DS + FR (n = 23))/CG (n = 11)/IC (Individuals capable of vigorous activity and aerobic activity/EC (Not reported).	Period 15 min (8 min)/ROM, Flexibility and CMJ (ankle)
De Camargo et al. (2021)/(RCES)/(Brazil)	Bike/(n = 10)/MA (26 ± 5 anos)/M.	EG ((FR (n = 10))/CG (n = 10)/IC (athletes 6 months training (distance 150 km/week)/EC (Not reported)	Period 5 min, (1min each muscular group)/ Muscular Power (Hamstring, Tibialis anterior and gastrocnemius)
Giovanelli et al. (2018)/(RCES)/(Turkey)	Running/(n = 13)/MA (26.3 ± 5.3)/F.	EG (n = 7)/CG (n = 6)/IC (Collegiate athletes of mountain running)/EC (Not reported).	Period 8min, 1min (each muscle group)/Velocity, (VO_{2max}); power of VJ and CMJ (Anterior plantar fascia, leg and posterior thigh muscles).
Healey et al. /(2014)/RCCT)/(Iceland)	Athletics (n = 42) MA/ (21.56 ± 2,04)/M. F.	EG ((SAFR (n = 42))/CG ((Platform (n = 42)/IC (training 3 to 4 times a week for the last 6 months, without alcohol, nicotine and caffeine)/EC (health problems that could affect your ability to complete the study).	Two days of testing with 1 day of MFR/power, VJ, strength and velocity (Hamstring, quadriceps)
HSU et al. (2021)/(RCCT)/(China)	Table tennis/(n = 23)/MA (11.2 ± 2.6)/M. F.	EG ((DS + FR (n = 23))/CG ((SS (n = 23))/IC (Professional Boxers)/EC (Amateur boxers; with neuromuscular diseases; taking medication).	Period 8 min of dynamic stretching combined with 12 min of intervention/Flexibility (Rotator cuff, Hamstring, hip flexors and erector spinae muscles).
Kim and Yim (2018)/(RCES)/(Korea)	Soccer/(n = 40)/MA: EG (16.4 ± 0.8 years)/CG (16.2 ± 0.7)/M.	EG ((IASTM (n = 20))/CG (n = 20)/IC (no illness)/EC (Not reported)	Period of 12 weeks (60 min each session)/ flexibility, height VJ, balance. (Plantar and dorsi ankle flexors)
Author/Year/Study Type/ Country	Sport/n/MA/Gender	EG/CG IC/EC	Intervention Period/Evaluated Outcome
Martins et al. (2024)/(RCES)/(Brazil)	Swimming/(n = 30) MA: (15 ± 2.6)/Not reported	EG (n = 10)/GS (n = 10)/CG (n = 10)/IC (Athletes who have been practicing sport for two years and attend at least four training sessions a week)/EC (surgical procedure in the last three months; limb amputation; cardio-respiratory disease).	5 weeks/scapular ROM, stroke frequency and stroke length in swimming (muscles of the shoulder girdle)
Rey et al. (2019)/(RCES)/(Spain)	Soccer/(n = 18)/MA (26.6 ± 3.7)/M.	EG ((FR (n = 9))/CG (n = 9) IC (Soccer professionals taking part in the training session)/ EC (serious injuries and individuals with experience in respiratory rate exercises)	Period of two experimental sessions of 20 min/ VJ, *sprint time* de 5 m e 10 m, flexibility (Hamstring, Quadriceps. Gluteus and gastrocnemius.
Richman et al. (2019)/RCCT)/(Colombia)	Volleyball and Basketball (n = 14)/MA (19,8 ± 1,3)/ F.	EG ((MFR + FR (n = 14))/CG ((DS (n = 14))/IC (Healthy, active women)/EC (Not reported)	2 sessions 5 min running. 1 session FR (6 min (MFR) or 6 (GW)/Sit and reach, VJ e CMJ (Hamstring e quadriceps)
Rhyu et al. (2018)/(RCES)/(Korea)	Basketball/(n = 40)/MA: (17.24 ± 1,71)/M.	EG ((IASTM (n = 20))/CG (n = 20)/IC (Basketball athletes)/ EC (Not reported)	Period 8 weeks/ROM_{active}; isokinetic strength of ankle and knee, velocity and flexibility (Hamstring, quadriceps)
Sağiroğlu et al. /(2017)/(RCES)/(Turkey)	(Judo, Karate, Tae Kwon Do, Muay Thai)/(n = 16)/ MA (23.9 ± 3.6)/M.	EG ((FR (n = 16))/CG ((SS (n = 16))/IC (Minimum 5-week training and hamstring shortening)/EC (no history of arthritis, meniscopathy or ligament injuries).	Period 8 min/CMJ and flexibility (quadriceps, gluteus and gastrocnemius.)
Seever et al. (2022)/(RCES)/(Germany)	Athletics/(n = 42)/MA (24.3 ± 2.5)/M. F.	EG ((MFR with FR (n = 21))/CG ((MFR (n = 21))/IC (regular physical activity twice a week or more)/EC (basal flexibility ≥18 cm on WBLT and Y-Balance test, recent injury to MMII).	Period 3 set 60 s per leg, 6 days a week for 2 weeks/ROM, balance (gastrocnemius, soleus and plantar)
Wang et al. (2022)/(RCES)/(China)	Tennis/(n = 27)/MA (20.4 ± 1.3)/M.	EG ((PVPD (n = 9))/CG (n = 9)/IC (Male tennis players/EC (musculoskeletal, traumatic and cardiovascular diseases)	Period 7 min/CMJ; reactive strength, lateral acceleration (low back muscles, gluteus, quadriceps)

Abbreviations: DS – Dynamic Stretch; ROM – Range of Motion; SS – Static Stretch; EC – Exclusion Criteria; IC – Inclusion Criteria; RCES – Randomized Controlled Experimental Study, RCCT – Randomized Crossover Clinical Trial; FR – Foam rolling; DS – Dynamic stretching; SAFR – Self-applied release foam rolling; PVPD: portable vibrational percussion device; CG– Control Group; EG – Experimental Group; GS – Group with mobilization without myofascial release; F – Feminine; M – Masculine; IASTM – instrument-assisted soft tissue mobilization; MA – Mean Age; n- Sample number; VJ – Vertical Jump; CMJ – Counter movement jump; VO_{2max} – Maximum oxygen volume; GW – Gentle walk; F – Feminine; M – Masculine; Min.- Minutes; MFR – Myofascial Release; n-sample number; MMII – Lower limbs; Teste Y-Balance – Functional test for clinical trial; WBLT – weight-bearing storage test.

SMR therapy for strength, speed and ADM in athletes; 3) Types of MFR applied by a therapist and SMR therapy for flexibility in athletes.

2.6. Assessment of bias risk in selected studies

Two authors conducted bias analysis independently and cross-checked by a third reviewer. Five criteria were considered using the Cochrane Handbook tool (RoB 2): a revised Cochrane risk-of-bias tool for randomized trials (Higgins et al., 2019). Verification was carried out by two assessors independently. Five criteria were considered for assessing RCT and RCCT included in the tool: (1) bias in randomization; (2) bias due to deviations from intended interventions; (3) risk of bias due to missing outcome data; (4) bias in outcome measurement; (5) bias due to selection of the reported result and other sources of bias. In the RoB 2 tool, bias risk in each domain is classified as follows: low risk of bias, high risk, and uncertain risk. For this study, scoring was adapted as follows: studies to be included should have a low risk of bias in three of the five RoB 2 domains, meaning studies with a minimum of 60%

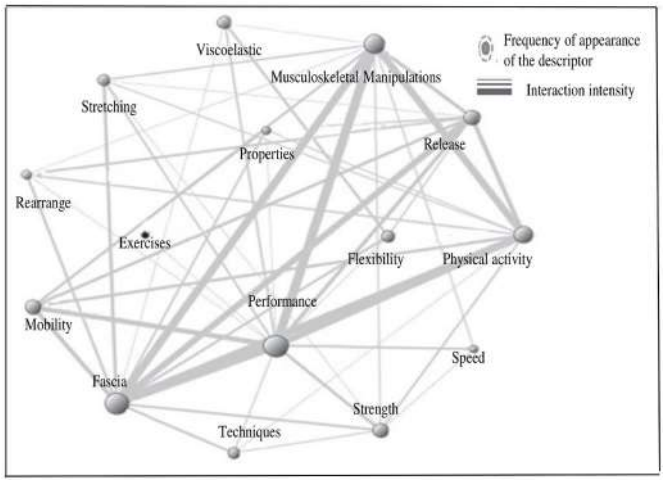

Fig. 2. - Analysis of interaction among the most relevant keywords. Software Sitkis (Schildt, 2002).

relative frequency of low risk of bias would be included. However, a low risk of bias in domains 1, 2, and 5 was essential. In case of disagreement, a third author conducted a new verification, as shown in Table 2.

3. Results

3.1. Studies selection

In the databases, 6203 records were identified. After removing 3299 duplicate, 2904 records remained for analysis. In the first stage of screening, there was a comprehensive analysis of titles and abstracts supported by the PICO question, excluding 2884 records, resulting in 20 scientific studies. Subsequently, two studies were retrieved through manual search and grey literature in Google Scholar. There were 28 eligible studies remaining for full-text reading, of which 12 were excluded from the analysis due to the following factors: eight had limited details in the methods section, two studies did not clarify the results on MFR in terms of statistical data, and two studies evaluated other outcomes not compatible with the purpose of the present study. In the inclusion stage, 16 scientific studies remained, as shown in Fig. 1.

Subsequently, the interaction of the descriptors present in the selected articles, as shown in Fig. 2.

3.2. General characteristics of research related to the type of study and the developed country

The present systematic review, after applying selection criteria as mentioned, obtained 16 scientific studies: 12 RCT and 4 RCCT. According to the country where the study was conducted, the distribution was as follows: Brazil 2 (12.5%), Turkey 2 (12.5%), South Korea 2 (12.5%), Colombia 2 (12.5%), China 2 (12.5%), Spain 1 (6.3%), United States of America (USA) (6.3%), Iceland 1 (6.3%), Japan 1 (6.3%), Germany 1 (6.3%), and United Kingdom 1 (6.25%), with further details in Table 1. Consecutively, the strategies used in the studies selected for qualitative analysis are shown in Table 2.

3.3. Absolute sum of data in relation to the number of searches and scores achieved

In relation to the scores of the scale regarding the use of the RoB 2 tool, eight scientific studies achieved low risk of bias in (4) domains, and eight studies obtained (3) domains, Table 3.

4. Discussion

4.1. Characteristics of fascia constitution and particularities arising from myofascial release (MFR)

The results following the application of Myofascial Release (MFR) in scientific literature have become renowned, showcasing reductions in pain and improvements in balance. These benefits are indicative of a promising feasibility in furthering MFR advancements (Adstrum et al., 2016; Schleip et al., 2019).

In the sports setting, one of the main advantages of using MFR lies in the viscoelastic properties of the muscular structure, as these properties can be altered through the implementation of different MFR techniques without causing a reduction in athletes' performance (Grieve et al., 2015). More recent studies also demonstrate the ability of MFR to reduce stiffness and alter viscoelastic characteristics (Kim and Yim, 2018; Rhyu et al., 2018; Leite et al., 2020). However, there is still a lack of protocols containing programs with methods and processes specific to MFR for the performance and recovery of athletes (Grieve et al., 2015).

To contemplate improvements in athletes' internal biomechanics, it is essential to identify not only the bodily structures set in motion but also to understand the internal biological components of the human body, inferring the tendon, muscle, bone, and ligament forces (Guillamón, 2014). Similarly, the understanding of the constituent factors of the fascia, such as the presence of type 1 endocannabinoid receptors and cytoplasmic vesicles rich in hyaluronic acid (HA), and how it manifests during its manipulation (Fede et al., 2022; Stecco et al., 2022). It is relevant to highlight the benefits of MFR related to the excreted content and extracellular matrix (ECM) and the advantages of increased tissue hydration, turbidity, and flexibility (Forteza et al., 2021; Fede et al., 2022; Stecco et al., 2022).

Additionally, thixotropy is another important property that can alter the viscoelastic properties of the extracellular matrix in tendons, fascia, and muscle. This property can decrease viscosity when agitated and can solidify when left at rest. Thixotropy is also present in fascia and is related to one of its main constituents, hyaluronan (Krause et al., 2017). Myofascial tone can be modulated with rollers by altering thixotropic properties, blood flow, and fascial hydration (Behm and Wilke, 2019). However, its viscosity can still be reduced under any applied load condition and may undergo changes (Krause et al., 2017).

Conceiving the types of MFR and their influence on the nervous system (NS) is fundamental, as is understanding the effects of mechanoreceptors contained within the fascia and musculature on central modulation, pain interpretation, and even the potential increase in endogenous hormones following technique management (Beardsley and Škarabot, 2015; Aboodarda et al., 2015). Another relevant factor is the values of oxyhemoglobin resulting from MFR techniques. One study revealed an increase in oxyhemoglobin after myofascial reorganization (MR) in the trapezius muscle (MT). Researchers employed near-infrared spectroscopy before and after a single MR intervention, with assessment after 10 min, showing an increase in oxyhemoglobin in the fibers - mean of MT (0.72 ± 1.47 vs. -0.14 ± 1.33 mmol/dL, $p = 0.01$) (Martins et al., 2024).

Understanding the morphological structure of the deep fascia is important, as it surrounds the muscles, gradually accumulating tensions over time, externally and internally affecting other soft joint components, eventually leading to a loss of functionality (Schleip and Müller, 2013; Guillamón, 2014; Myers, 2009). Scholars have investigated balance through tactile stimulation using stabilometry and plantar pressure (Martínez-Jiménez et al., 2020). The results indicated improvements in balance by restoring normal tension to the plantar fascia, likely due to the morphological structure and proprioceptive functions contained within it, such as high innervation and a dense quantity of mechanoreceptors and sensory nerve endings (Martínez-Jiménez et al., 2020).

Therefore, the main purpose of MFR is to reduce fibrous adhesions in facial networks and subsequently reverse the energy caused by

Table 2
Strategies of the selected studies for qualitative analysis.

Author/year	Intervention Strategies
Afanador-Restrepo et al. (2023)	The Range of Motion (ROM), jump height and flight time, strength and dynamic flexibility were assessed using the Goniometer Pro, the CMJ protocol in the OptoGait, 1 Repetition Maximum, Average Propulsive Velocity, and Sit and Reach test, respectively.
Behara and Jacobson (2017)	Each dependent variable (vertical jump power and velocity, isometric knee torque, and hip ROM) was evaluated. Each variable was assessed before and after: (a) no treatment, (b) deep tissue foam rolling, (c) dynamic stretching.
Bond et al. (2019)	The changes in strength gains were compared between a control group following a strength training regimen (n = 10) and a treatment group (n = 10) following the same strength routine along with a fascial system exercise protocol.
Blades et al. (2022)	The ankle dorsiflexion range of motion (ADF-ROM), sit-and-reach, countermovement jump (CMJ), and squat jump (SJ) were assessed. Participants either sat inactive for 10 min (control) or performed FR of the lower limbs totaling 30 s (30FR) or 60 s (60FR) targeting four agonist-antagonist leg muscles. The test was then repeated before and after a simulated preparatory period of 15 min of inactivity following warm-up to establish the acute and delayed effects of static stretching on performance.
De Camargo et al. (2021)	Two groups of cyclists were separated for one week before performing a 3-min total cycling test: foam rolling or control. During the foam rolling protocol, participants were instructed as follows: roll back and forth on one leg and place the opposite leg crossed from the proximal to the distal portion of the rectus femoris and vastus lateralis. Only one 60-s set for each muscle group was performed. The perceived sensation scale (10 min pre and post-test), the CR-10 subjective effort perception scale (10 min post-test), pressure pain threshold (pre and 24 h post-test), and average-maximum power were utilized.
Giovanelli et al. (2018)	The effect of FRSMR on energy cost of running and lower limb muscle power during squat jump and CMJ was measured. Assessments were conducted before (PRE), immediately after (POST), and 3 h after (POST 3 h) an FRSMR protocol (experimental condition). In the control condition testing session, the same measurements were taken without undergoing the FRSMR protocol. Experimental and control conditions were tested in a randomized order.
Healey et al. (2014)	A series of plank exercises or foam rolling exercises was performed, followed by a series of athletic performance tests (vertical jump height and power, isometric strength, and agility). Fatigue, pain, and effort were also measured. A 2 × 2 (trial × gender) repeated measures analysis of variance with appropriate post hoc analysis was used to analyze the data.
Hsu et al. (2021)	Players performed 3 different interventions in random order (DS + SS, DS + FRSMR, and DS + VFR). The target muscle groups included bilateral posterior calf, posterior thigh, anterior thigh, back, and shoulder. The following tests were performed: sit and reach for flexibility, plank jump for lower limb power, medicine ball throw for upper limb power, Edgren Side Step test for agility, and table tennis ball speed for speed were evaluated before and after the intervention.
Kim and Yim (2018)	Two groups, one assisted by instrument soft tissue mobilization and one control, completed various tests to determine player development. Isokinetic ankle power (i.e., dorsiflexion, peak torque of body weight at angular velocities of 30°/s and 120°/s for both right and left feet; plantar flexion, peak body weight torque at angular velocities of 30°/s and 120°/s for both right and left feet) and knee (extension, peak body weight torque at 60°/s and 180°/s for right and peak left-body weight torque at 60°/s; flexion, peak body weight torque right and left at 60°/s and 180°/s), muscle fatigue, and physical fitness were evaluated.
Author/year	Estratégia de intervenção
Martínez-Jiménez et al. (2020)	A manual technique involving bilateral pressure and traction was performed on the plantar fascia. The control group (CG) underwent tactile stimulation. Participant position, therapist position, and application time of the techniques (5min) were the same for both interventions. Main outcome measures: We assessed stabilometry variables and static footprint. The footprint variables were divided into rearfoot, midfoot, and forefoot areas.
Rey et al. (2019)	The effectiveness of FR interventions (20 min of FR exercises on the quadriceps, hamstrings, adductors, glutes, and gastrocnemius) and passive recovery (20 min seated on a bench) immediately following a total training session was assessed. Jump performance, agility, sprint, and flexibility were evaluated 24 h after the training. During two experimental sessions, 18 professional soccer players (age 26.6 ± 3.3 years; height: 180.2 ± 4.5 cm; body mass: 75.8 ± 4.7 kg) were tested.
Richman et al. (2019)	Two test sessions consisting of 5 min of self-paced running, followed by a 6-min foam rolling or light walking session, and a subsequent 6-min specific sport dynamic stretching (DS) period. Sit and reach tests were conducted after a general warm-up, the SMR or LW session, and after the DS. Participants performed 3 squat attempts. Jump tests (SJ, CMJ, drop jump) were observed. Two additional tests, the T-test of agility and a 10-yard short sprint, were then conducted.
Rhyu et al. (2018)	Asymptomatic basketball players were treated with IASTM six times per week for 8 weeks. The remaining 20 participants did not receive any treatment intervention between tests and served as controls. Ankle range of motion (two knee positions at 0° and 45° flexion), knee and ankle functional fitness (lateral step and vertical jump), and peak isokinetic torque were determined during ankle dorsiflexion and plantar flexion, and knee extension and flexion.
Sağiroğlu et al. (2017)	Combat athletes performed three sessions of AR exercises, (AR + SS), and (AR + SMR) at 48-h intervals in a randomized crossover design. After each session, the subjects performed sit-and-reach tests and CMJ successively with 30 s of rest between tests at the 15th second and at the 2nd, 4th, 6th, 8th, 10th, 15th, and 30th minutes during the recovery period.
Seever et al. (2022)/(RCES)/(Germany)	The ankle range of motion (ROM) was assessed using the Weight-Bearing Lunge Test (WBLT), and dynamic balance was assessed using the Y-Balance Test for both lower limbs. The foam rolling (FR) group was instructed to roll their calf muscles for three sets of 60 s per leg, six days a week, for two weeks. Acute effects were measured during the initial dorsiflexion ROM and dynamic balance tests immediately after foam rolling. Chronic and residual effects were measured 1 day and 7 days after the intervention period.
Wang et al. (2022)	The acute effects of VFR and PVPD on the athletic performance of tennis players during warm-up were compared. Specifically, the countermovement jump (CMJ), reactive strength index (RSI), and hexagon test (HT) were assessed.

Abbreviation: AR – Aerobic running, AROM - Active range of motion, CMJ - countermovement jump, DS - dynamic stretching, FR - Foam rolling - FRSMR - Self-applied release with foam rolling, IASTM - instrument-assisted soft tissue mobilization, LW - light walking, MMII – Lower limbs, MMSS – Upper limbs, PVPDs - commercial portable vibration percussion devices, SS - Static stretching, SJ - Squat jump, SMR - Foam rolling session, RM - roller-massage, ROM – Range of motion, VJ – Vertical jump, VFR - Vibration foam rolling, WBLT - Weight-bearing lunge test.

mechanical stress (Nordez et al., 2017). In light of this, one must consider the possibilities of mechanical adaptations following interventions of chronic stretching that may occur at the fascial level. Among others, the resistance to stretching that presents itself differently among fascia, tendons, and muscles due to the different mechanical properties of the tissues (Nordez et al., 2017).

4.2. Types of MFR applied by a therapist and SMR therapy for strength, speed and ADM in athletes

The FRSMR is a technique that has been used with favorable results for muscle strength (Santa Cruz et al., 2017; Bond et al., 2019; Hsu et al., 2021). When testing the CMJ height in athletes after the FRSMR maneuver, values are increased in the reactive strength index and hexagon test along with the drop jump test (Sağiroğlu et al., 2017; Giovanelli et al., 2018; Blades et al., 2022; Wang et al., 2022). Similarly, in the

Table 3
EECR and ECRC studies according to the Cochrane Handbook (RoB2) scale adaptation.

No.	First author	Cochrane Handbook (RoB 2) SO/MS	Relative Frequency (%)
01	Afanador-Restrepo et al.	4/5	80.0
02	Bond et al.	3/5	60.0
03	Blades et al.	4/5	80.0
04	Behara et al.	3/5	60.0
05	Camargo et al.	3/5	60.0
06	Giovanelli et al.	3/5	60.0
07	Healey et al.	3/5	60.0
08	HSU et al.	4/5	80.0
09	Kim e Yim	4/5	80.0
10	Martins et al.	3/5	60.0
11	Rey et al.	4/5	80.0
12	Richman et al.	3/5	60.0
13	Rhyu, Han e Rhi.	4/5	80.0
14	Sağiroğlu et al.	3/5	60.0
15	Seever et al.	4/5	80.0
16	Wang et al.	4/5	80.0

Abbreviations: SO: score obtained; MS: maximum score.

CMJ, significant values were observed immediately after treatment with 3 h at 200 ms in the initial force execution phase (+38.9%) (Giovanelli et al., 2018; França et al., 2023).

When the SMR was used for runner athletes, the applicability of the FRSMR indicated increased outcomes in the comparison between pre- and post-training, with maximum muscle power of the lower limbs (quadriceps, glutes, and gastrocnemius) immediately after the end of post-training (+7.9% ± 6.3%) and, after 3 h (+10.0% ± 8.7%) (Giovanelli et al., 2018; França et al., 2023). In contrast, scientific findings showed negative outcomes with the FRSMR maneuver: one study observed a reduction of 0.95 (95% CI: 0.94–0.97) in the SMR 24 h after the application of the technique (Rey et al., 2019). Another research identified the possibility of FRSMR stressing the tendon (Schleip, 2003). There is limited clinical data on the mechanism of this treatment with FRSMR in athletic performance, mainly on the optimal timing of its use to achieve more significant results for power, stroke volume, strength, and speed of athletes (Healey et al., 2014).

Another proposal was IASTM, which has been used in active range of motion (ROMactive) in basketball athletes, indicating greater isokinetic strength in the ankle. The results showed an increase in ankle isokinetic strength and power, resulting in angular velocities of 30°/s and 120°/s for plantar flexion and dorsiflexion, and knee strength at 60°/s and 180°/s for knee flexion and extension (Rhyu et al., 2018). A study using foam rolling demonstrated that both acute and chronic effects were significant for ankle dorsiflexion range of motion ($p < 0.05$) (Seever et al., 2022).

In the comparison of the residual effects of aerobic running (AR) combined with self-myofascial release (AR + SMR) versus AR + static stretching (SS), the outcomes showed no significant differences between the techniques ($p > 0.01$). However, in the CMJ, the results were superior at the 10-min mark with AR + SMR ($p < 0.01$) (Sağiroğlu et al., 2017).

The ROM of the shoulder complex joint presents a strong dependency impact with the scapulothoracic joint, MFR applied by the therapist. A recent study with butterfly stroke swimmers instituted randomization into three groups: the first group (IG) received scapular mobilization with MFR applied to the subscapularis muscle by the lateral edge of the scapula and rib cage mobilization; the second group (FG) performed scapular mobilization without MFR of the subscapularis muscle and without rib cage mobilization, and the third group control (CG), without any intervention. The results showed the importance of using applied MFR, with FG showing a significant reduction pre and post-intervention: in the average speed pre ($p = 0.002$) and post ($p = 0.02$); in the stroke frequency pre ($p = 0.002$) and post ($p = 0.003$); and stroke length pre ($p = 0.01$) and post ($p = 0.05$) (Martins et al., 2024). The outcomes pointed out a warning to swimming professionals about the possibility of negative outcomes when using manual therapy through scapular release without applied MFR, as the FG presented a significant decrease in the indicators of average velocity, stroke frequency, and stroke length in swimming (Martins et al., 2024). There are considerations to be taken into account, such as the specificities regarding the applicability of the techniques respecting the impact of scapular displacement and collagen tissue responses during the maneuver.

4.3. Types of MFR applied by a therapist and SMR therapy on flexibility in athletes

Although MFR techniques exhibit promptness in responses, their mechanical structural content is not yet fully elucidated, as the preceding and current literature still lacks necessary elements to support this mechanism (Beardsley and Škarabot, 2015; Forteza et al., 2021; Fede et al., 2021; Stecco et al., 2022). To date, it is understood that MFR may potentially favor health, given that the intrafascial structure is sensitive to pressures and tangential forces (Bond et al., 2019).

However, the process of remodeling facial structures seems to allow greater flexibility, whether passively or actively, strategies enable the reorganization of piezoelectricity, facial adhesions, and tissue viscoelasticity, which in turn, is composed of collagen and elastin (Beardsley and Škarabot, 2015). The viscoelastic properties of the muscle are activated with increased blood flow and temperature, with FRSMR being one of the proposals to prevent densification and avoid increased solid state and/or limitation of fascia viscosity (Knight et al., 2001). It is worth noting the results of a current study using a technique for the experimental group (EG) (Orthopedic Manual Therapy Oriented (MOT) + FR and control group (CG) (only FR). The scholars identified that the therapy combined with FR is better applied for muscle power, strength, and flexibility, while FR alone is better indicated for flexibility (Afanador-Restrepo et al., 2023). A study identified reduced value for lower limb flexibility with the use of FRSMR, indicating an intraclass correlation coefficient (ICCs) of 0.99 (95% CI: 0.97–0.99) (Rey et al., 2019).

Another study using the Thomas test found that using the FR technique can lead to gains in joint range of motion without altering muscle length (Vigotsky and Bruhns, 2015). However, the application time is strongly associated with muscular performance, considering both power values and ROMactive (De Camargo et al., 2021; Shalamzari et al., 2022). The adaptation time of the fascia, i.e., the estimates regarding the chronological organization of management, may be a crucial particularity to be observed. A study conducted with healthy individuals aged between 30 and 60 years, in a weight training program, using a 10-week protocol and following the guidelines of the American College of Sports Medicine (ACSM), proved to be not significant for improving strength (Bond et al., 2019).

In general, MFR presents a favorable prognosis, whether used in isolation or as a supplement. A study aimed at verifying the flexibility of the hamstrings in young adults identified an average flexibility gain between the Stretching Group (SG) versus the Stretching + MFR Group (STG). The STG Group in the Active Knee Extension Test (AKET) showed a 23.15-degree increase with an increase in the Sit and Reach Test (SRT) on the Wells Bench of 8.7 cm. On the other hand, the stretching group GA without MFR obtained an average gain of 13.7° in the AKET and an increase of 2.3 cm in the SRT. Thus, the results of this study demonstrated superior gains for the STG group (Ferreira et al., 2021). A similar study compared SMR to static stretches (SS) on the hamstring muscles, similarly obtaining superior acute gains with SMR (Carvalho et al., 2017). Although for horizontal jump (HJ) in university athletes, MFR applied by a professional over a 90-s period did not indicate significant values for the hamstring (Queiroga et al., 2021).

The MFR, when applied by a professional compared to MFR techniques using a tennis ball or FRSMR, suggests greater impact on outcomes when the purpose is pain relief (Oliveira et al., 2019). However,

positive parameters were established with the isolated use of both technique modalities. In using MFR for the flexibility of the hamstrig and spinal mobility, a group of researchers used a tennis ball for the technique and the Wells bench for flexibility measurement. The outcomes were significant ($p < 0.01$) (Santa Cruz et al., 2017). Similar results were found using the intervention with FRSMR, where the outcomes indicated greater flexibility and strength of the EG compared to the CG that performed SS (Sousa et al., 2017).

The FRSMR can be used to improve ROM, propulsion force, and speed without compromising flexibility. A study using foam rollers on the quadriceps musculature of adolescent squash players for 60 s was found to be relevant for hip flexor flexibility ($P = 0.03$) ($p < 0.05$) (Murray et al., 2016). Similar effects were observed for hip flexibility after dynamic stretching and FR ($p < 0.01$), although no changes in strength or power were evident in a similar study (Behara and Jacobson, 2017). However, a more contemporary study has shown that MFR in the form of foam rolling after a general warm-up and before a dynamic stretching session (DS) appears to be more favorable for sports with a higher frequency of vertical jumps (VJ) and CMJ, as it does not impair athletes' flexibility (Richman et al., 2019).

This systematic review had some limitations, such as the limited sample size in different studies, contributing to selection bias, and although ensuring internal validity, they hindered the generalization process. Thus, the conceptions for the specific applicability of techniques for the respective types of sports modalities became more restricted. Another factor was the limited exclusion criteria in 4 scientific studies, which turned the analysis more complex and difficult for their inclusion in the research.

5. Conclusion

The techniques involving applied or self-applied MFR aimed at improving strength, speed, ROM, and flexibility lack consensus regarding their applicable period, due to difficulties in identifying the ideal applied tension load, temperature level, and viscoelastic properties during the release process of the deep fascia. However, improvements in oxygenation, piezoelectricity reorganization, and fascial tension normalization have become evident after MFR.

Regarding strength, speed, and ROM, isolated IASTM and MFR combined with other techniques appear as favorable predictors for better results in the lower limbs, but isolated MFR requires further investigation. Regarding flexibility, there is a contrast of results with the use of isolated FRSMR, although it may prevent densification, the technique suggests improvements in muscle strength acquisition without compromising flexibility. MFR applied by a professional provided a more flexible quality for scapular mobilization, whether isolated or in combination with other techniques, but its best indication and/or specific applicability is for pain reduction.

Ethical approval

Not applied.

CRediT authorship contribution statement

Maria Elisa Duarte França: Writing – original draft, Investigation, Formal analysis. **Mayane dos Santos Amorim Botti:** Writing – review & editing. **Francisco Camolesi Ide:** Writing – original draft, Investigation, Formal analysis. **Larissa Sinhorim:** Writing – original draft. **Gilmar Moraes Santos:** Writing – review & editing, Methodology, Formal analysis. **Iramar Baptistella do Nascimento:** Writing – review & editing, Methodology, Formal analysis.

Declaration of competing interest

The authors have no conflicts of interest to declare. All co-authors have reviewed and agree with the contents of the manuscript, and there is no financial interest to report.

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Effects of myofascial reorganization associated with kinesiotherapy on chronic pain and functionality of breast cancer survivors: development of a study protocol

Efeitos da reorganização miofascial associada à cinesioterapia na dor crônica e funcionalidade de sobreviventes de câncer de mama: desenvolvimento de um protocolo de estudo

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Abstract

Introduction: Breast cancer is the most common type of cancer among women. Treatments can lead to complications modifying upper limbs movement patterns and generating pain and functionality loss. Kinesiotherapy and myofascial reorganization (MR) have shown positive effects reducing chronic pain and improving upper limbs function. We hypothesize that these techniques can maximize results and reduce treatment time in clinical practice. **Objective:** To develop a study protocol to verify whether MR associated with kinesiotherapy is more effective than isolated kinesiotherapy to treat chronic pain and upper limb dysfunction in breast cancer survivors. **Methods:** Participants will be divided into two groups: intervention group (myofascial reorganization + kinesiotherapy) and sham group (traditional massage + kinesiotherapy). Six treatment sessions (once a week) and three-time assessment will occur. Instruments for assessing pain and functionality will be Visual Analogue Scale, Body Pain Diagram, Disabilities of the Arm, Shoulder and Hand Questionnaire, and goniometry. Statistical analysis will be conducted based on intention-to-treat analysis. To analyze the difference of means between groups, we will use T-Student or U Mann-Whitney test. Repeated measures ANOVA will be used to check treatments effects. Significance level for all tests will be 5%. **Conclusion:** We believe that the developed study protocol will show that MR associated with kinesiotherapy improve chronic pain and upper limbs functionality of breast cancer survivors.

Keywords: Breast cancer. Chronic pain. Functionality. Manual therapy. Physiotherapy modalities.

Resumo

Introdução: *O câncer de mama é o tipo de câncer mais comum entre as mulheres. Os tratamentos podem levar a complicações, modificando os padrões de movimento dos membros superiores e gerando dor e perda de funcionalidade. A cinesioterapia e a reorganização miofascial (RM) têm demonstrado efeitos positivos na redução da dor crônica e na melhora da função dos membros superiores. A hipótese do presente estudo é que essas técnicas podem maximizar os resultados e reduzir o tempo de tratamento na prática clínica.* ***Objetivo:*** *Desenvolver um protocolo para verificar se a RM associada à cinesioterapia é mais eficaz do que a cinesioterapia isolada no tratamento da dor crônica e disfunção do membro superior em sobreviventes de câncer de mama.* ***Métodos:*** *As participantes serão divididas em dois grupos: grupo intervenção (reorganização miofascial + cinesioterapia) e grupo* sham *(massagem tradicional + cinesioterapia). Serão realizadas seis sessões de tratamento (uma vez por semana) e três avaliações. Os instrumentos de avaliação da dor e da funcionalidade serão a Escala Visual Analógica, o Diagrama de Dor Corporal, o Questionário de Deficiências do Braço, Ombro e Mão e a goniometria. A análise estatística será realizada com base na análise de intenção de tratar. Para analisar a diferença de médias entre os grupos, serão utilizados o teste T-Student ou U Mann-Whitney. ANOVA de medidas repetidas será utilizada para verificar os efeitos dos tratamentos. O nível de significância para todos os testes será de 5%.* ***Conclusão:*** *Espera-se que a RM associada à cinesioterapia melhore a dor crônica e a funcionalidade dos membros superiores de sobreviventes de câncer de mama.*

Palavras-chave: *Câncer de mama. Dor crônica. Funcionalidade. Terapia manual. Modalidades de fisioterapia.*

Introduction

According to the World Health Organization (WHO), breast cancer is the most commonly diagnosed cancer.[1] Breast cancer treatments can lead to several complications: scar adhesions, tissue fibrosis, reduced range of motion (ROM), reduced upper limb muscle strength, and pain.[2] These factors, alone or in combination, change the upper limbs movement patterns and might lead to chronic pain and reduced functionality, affecting these women quality of life and daily living activities.[2-4]

Chronic pain after breast cancer surgery is one of the most common complaints, with a prevalence ranging from 20% to 68%.[5-7] Different mechanisms might be involved (nociceptive, neuropathic, central sensitization, and/or allodynia) and can make chronic pain treatment a challenge in clinical practice.[8] Due to chronic pain mechanisms complexity and multifactorial nature, there is no consensus in literature about the best therapeutic modality to treat this condition in women after breast cancer,[9] which intrigues researchers and clinicians.

Another common complication after breast cancer surgery is the reduced upper limb function, with a prevalence rate of over 50%.[2,10,11] Some factors are associated with worsening of upper limb function, such as pain intensity and characteristics, reduced shoulder flexion and abduction ROM, and decreased upper limb muscle strength.[11]

Literature suggests chronic pain treatment should be based on multidisciplinary approach involving pain education, psychopharmacological and physical therapy interventions.[12] Techniques like kinesiotherapy, stretching, strengthening, and neuromuscular control exercises can increase mobility and reduce shoulder pain.[9] Also, kinesiotherapy has shown positive effects for reducing chronic pain and increasing upper limbs functionality.[9,12] On the other hand, more than one intervention can be effective for the same symptom and these effects depend not only on the intervention type, but also on how and when it is applied.[9] The type, frequency, intensity, and ideal exercises duration are still not clear enough, as well as their effects in combination with other modalities in the treatment of the same symptoms.[9,13] Thus, two techniques association might lead to greater benefits.

Myofascial reorganization (MR) is a method of myofascial manual therapy which emphasizes: (i) diagonal pressure; (ii) shear loading; (iii) tensile loading; (iiii) compressive loading in the myofascial tissue. It aims to influence receptors in the fascia, contributing to changes in local fluid dynamics, capillary constriction and increased local blood flow, restoring normal integrity of treated tissue.[14] Thus, MR may reduce pain and improve body structures mobility and function.[15-17] In addition, manual contact is safe and reduces costs,[18] given the wide clinical applicability. Although current evidence indicates the effectiveness of interventions in fascial system, there are scarce high-quality methodological articles with large sample sizes,

requiring new studies to understand the role of available techniques.[19]

As there is insufficient information and no consensus on optimal chronic pain management and upper limb functionality among breast cancer survivors, we hypothesize that by combining benefits of two therapies we can maximize results and reduce treatment time in clinical practice. Therefore, this study aims to develop a study protocol to verify whether MR associated with kinesiotherapy is superior to isolated kinesiotherapy in chronic pain treatment and upper limb dysfunction in breast cancer survivors.

Methods

This study was approved by the Ethics Committee on Research with Human Beings (CEPSH) of the Universidade do Estado de Santa Catarina (UDESC), under CAAE protocol 10420519.7.0000.0118, and has been registered on the Clinical Trials platform under the protocol NCT04084600.

Study design

The study described in this protocol will be a double blind randomized controlled clinical trial (assessor and patient), parallel in two groups (IG - intervention group; and SG - sham group), organized according to the flowchart below (Figure 1). The protocol was developed according to the SPIRIT (Standard Protocol Items: Recommendations for International Trials) checklist, 2013.

All participants who agree to be part of the study will make the initial evaluation after signing the Informed Consent Form.

Setting and recruitment procedures

Data collection will be carried out in a reserved room at the Physiotherapy School Clinic of UDESC, in Florianópolis, Brazil. Women will be recruited by our research group through folders, banners, social media, and in person at the College of Health and Sport Science (CEFID) of UDESC.

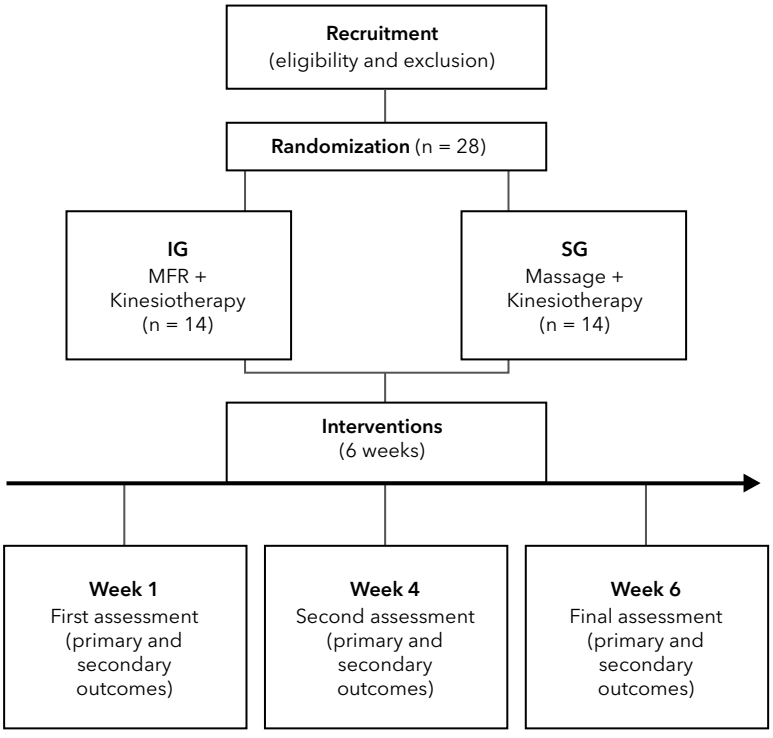

Figure 1 - Study flowchart.

Note: IG = intervention group; SG = sham group; MFR = myofascial reorganization.

Randomisation and blinding procedures

Participants will be randomly assigned to the IG or SG groups. Randomization will be carried out when recruitment procedures were finished through a random numerical sequence generated on Randomizer.org, in blocks, with an allocation rate of 1:1. Participants allocation will be hidden in sequentially sealed, numbered opaque envelopes prepared before the study starts. A researcher, who will not be involved in the other trial stages, will be responsible for randomization and allocation procedures. There will be three researchers responsible for assessments and they will not have access to participants allocation. The physiotherapist responsible for the interventions will not participate in assessments or participants allocation.

Participants

The sample will be composed of women who meet the following inclusion criteria: (1) age over 18 years; (2) have undergone breast cancer surgery; (3) have completed chemotherapy and/or radiotherapy; (4) present pain in the affected upper quadrant of the surgery for at least three months, with a minimum score of four-cm on the visual analogue scale (VAS) in the last week; (5) present a score of at least 30 in the DASH questionnaire (Disabilities of the arm, shoulder and hand).

Participants who present one of the following criteria will be excluded: (1) difficulty in understanding the Portuguese language to answer the questionnaires; (2) bilateral surgery for the treatment of breast cancer; (3) palliative care; (4) pregnant women; (5) use of analgesic and/or anti-inflammatory drugs; (6) rheumatic diseases; (7) history of orthopaedic surgery in the upper limbs; (8) have undergone physiotherapy treatment for less than 30 days.

Initial assessments

Women who agree to join the study will sign a Free Informed Consent Form and will be notified of the possibility to withdraw from the research at any stage. All participants personal identification data will be preserved according to national health council resolution, considering the possibility of results scientific dissemination. None of the participants will receive financial support to participate in the research.

Assessments will be conducted by three different physiotherapists, blinded and properly trained. Initially, in a face-to-face interview, a sociodemographic and clinical-surgical form will be fulfilled. Sociodemographic items include: name, age, education, marital status, ethnicity, living habits, physical activity, limb dominance, gynaecological history, gestational history and family income. For clinical-surgical aspects, type of breast cancer, cancer side, type of surgery, date of diagnosis, lymph node resection, other previous treatments and complications reported will be assessed.

Outcomes

Assessments will take place in three stages: just before the first treatment session (week 1), immediately after four treatment sessions (week 4), and at the end of the last treatment session (week 6). The primary outcome will be pain intensity and frequency measured by the VAS and the Body Pain Diagram (BPD). The secondary outcome will be upper limbs functionality by DASH and ROM, identified by the mean of the goniometry values.

VAS is a valid and reliable scale, widely used to identify pain intensity.[20,21] It consists of a numbered line from 0 to 10, 0 being no pain and 10 being the worst pain imaginable. BPD is a graphic representation of a woman's body in anterior, posterior and lateral view, created by Zomkowski et al.,[22] in order to identify the site and frequency of pain. In this diagram, women should mark their principal pain areas at the moment with an X. For the frequency analysis of pain location, the BPD will be segmented into five areas: anterior trunk, posterior trunk, lateral trunk, affected upper limb, and unaffected upper limb.

DASH will be used to assess the disabilities and physical symptoms of the upper limbs. It was created in Canada in 1996[23] and translated and validated in Brazil in 2005.[24] It is a 30-item questionnaire that assesses physical disabilities and upper limbs symptoms in a wide variety of musculoskeletal disorders. The score is a Likert scale ranging from one to five and the total score goes from 0 to 100, where higher scores represent higher physical disabilities and upper limbs symptoms. The questions refer to the last week and the items in the questionnaire are categorised into the domains: physical function, symptoms and social function.

For goniometry, a plastic manual goniometer with two adjustable arms will be used, which has proved to be

a valid and reliable tool.[25] The active ROM of the shoulder joint will be objectively measured in flexion, abduction, internal and external rotation movements. Participants will be positioned according to Marques,[26] and will perform two repetitions of each movement; the mean of these measures will be considered for the analysis of the results.

Interventions

Participants will undergo six treatment sessions once a week for six weeks, each lasting 40 minutes. The sessions will be conducted individually in a reserved room with adequate lighting and air conditioning adjusted to a temperature of approximately 23 °C. The interventions will be applied by a physiotherapist with previous experience and practice in this protocol. The interventions proposed for each group are described in more details below:

Intervention group

First, a 20-minute MR protocol will be conducted using an adapted approach described in Sinhorim et al.[14] The techniques will be applied emphasizing shear loading, tensile loading and compressive loading, as shown in Table 1 and Figure 2.

Table 1 - Description of myofascial reorganization protocol for breast cancer survivors

Techniques sequence	Techniques description
A. Sternal region	Participant: supine position with knees bent. Therapist: standing in front of the participant's head. Technique: the therapist fixes one hand in the region of the nuchal ligament and the other hand over the sternum, making a smooth and progressive caudal pressure towards the stretcher (1 minute).
B. Anterior ribcage region	Participant: supine position with knees bent. Therapist: standing in front of the participant's head. Technique: the therapist performs pressure and sliding from the xiphoid process, passing through the sternum, the infra clavicular region and ending at the acromion (6 times).
C. Diaphragm reorganization	Participant: supine position with knees bent. Therapist: standing beside the stretcher, in front of the participant's pelvis. Technique: the therapist performs pressure and sliding from the xiphoid process to the lower borders of the last ribs (6 times).
D. Pectoralis major	Participant: supine position with knees bent. Therapist: standing beside the stretcher, in front of the participant's chest. Technique: the therapist fixes one hand on the humerus and applies pressure towards the sternum with the other hand (1 minute).
E. Scapular region 1	Participant: lateral position, without pillow and with 90° of knee and hip flexion. Therapist: standing beside the stretcher, in front of the participant's abdomen. Technique: therapist performs pressure and sliding on the medial and upper border of the scapula (6 times).
F. Scapular region 2	Participant: lateral position, without pillow and with 90° of knee and hip flexion. Therapist: standing beside the stretcher, in front of the participant's abdomen. Technique: therapist departs the scapula from the ribcage and performs scapular mobilization in eight (1 minute).
G. Scapular region 3	Participant: lateral position, without pillow and with 90° of knee and hip flexion. Therapist: standing beside the stretcher, in front of the participant's abdomen. Technique: the therapist places the thumb in the region of teres minor muscle and applies sustained pressure (1 minute).
H. 45° Lateral trunk	Participant: lateral position, without pillow and with 90° of knee and hip flexion. Therapist: standing beside the stretcher, in front of the participant's posterior thorax. Technique: therapist with hands overlapped at 45 ° with the lateral region of the participant's thorax, performs pressure between the 6th and 8th ribs towards the stretcher and shoulder of the participant (1 minute).
I. Lateral trunk region	Participant: lateral position, without pillow and with 90° of knee and hip flexion. Therapist: standing beside the stretcher, in front of the participant's posterior thorax. Technique: therapist positions one hand on the upper thorax and the other on the lower thorax, the upper hand remains fixed and the lower one moves in a caudal direction (1 minute).
J. Thorax reorganization	Participant: lateral position, without pillow and with 90° of knee and hip flexion. Therapist: standing beside the stretcher, in front of the participant's posterior thorax. Technique: therapist places one hand on the anterior region of the last ribs and the other hand in the region of the inferior angle of the scapula, applying twisting pressure in a cranial direction (1 minute).

Immediately after MR protocol, participants will undergo a 20-minute kinesiotherapy protocol. This protocol was created based on previous studies,[9,27-29] and consists of stretching, strengthening, control, and stabilization exercises of shoulder complex, according to Table 2 and Figure 3.

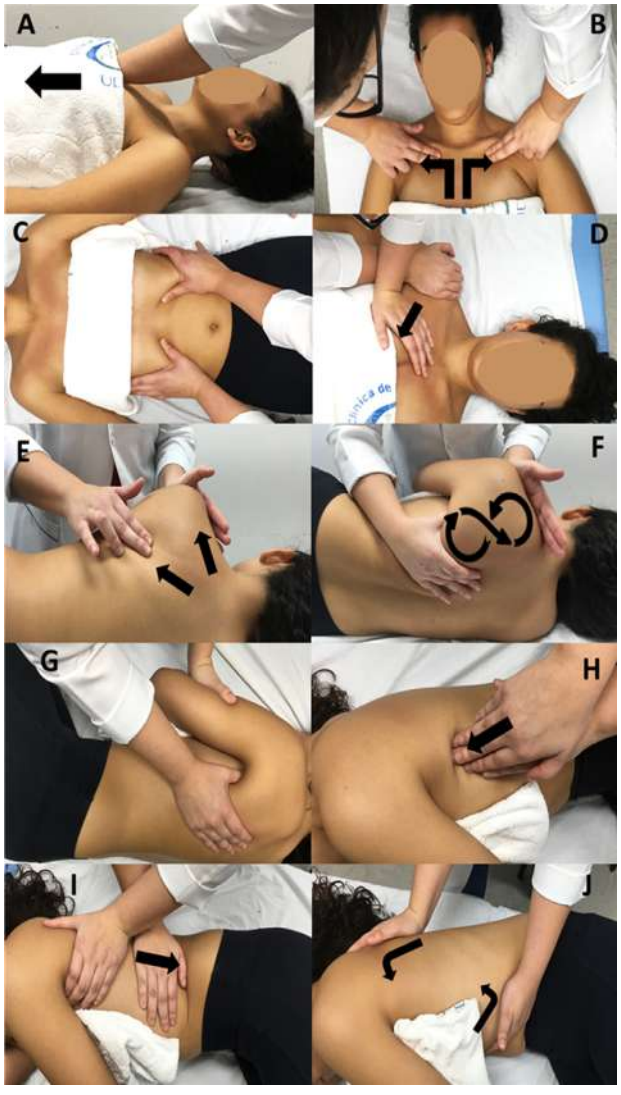

Figure 2 - Myofascial reorganization protocol for breast cancer survivors.

Note: A - Sternal region; B - Anterior ribcage region; C - Diaphragm reorganization; D - Pectoralis Major; E - Scapular region 1; F - Scapular region 2; G - Scapular region 3; H - 45° Lateral trunk; I - Lateral trunk region; J - Thorax reorganization.

Table 2 - Description of the kinesiotherapy protocol for breast cancer survivors based on stretching, strengthening, control and stabilization of shoulder complex

Exercises sequence	Exercises description
1. Stretches	Seating, participants will stretch pectoral, levator scapulae, trapezius and latissimus dorsi. Each position will be held for 1 minute and 30 seconds.
2. Codman's pendulum exercise	Participants will stand with torso flexed over hips at 90° and one arm hanging in a 60° to 90° flexion or abduction position in the scapular plane. Participants will perform circling movements for 1 minute and 30 seconds. Dumbbells up to 1 kg will be used.
3. Scapular mobilization	Participants will stand, face the mirror and perform scapular adduction, abduction, elevation and depression movements. 1 set of 10 repetitions for each movement.
4. Shoulder flexion and abduction	Participants will stand, close to the wall, performs flexion and abduction movements in the scapular plane, sliding her hands along the wall. 1 set of 10 repetitions for each movement.
5. Shoulder elevation with dumbbells	Participants will stand, performs scapular elevation and depression with arms parallel to the body holding dumbbells. 2 sets of 10 repetitions. Dumbbells up to 1 kg will be used.
6. Seated chest press with dumbbells	Participants will be seated with upper limbs in 90° of shoulder flexion and full elbow extension, with pronated forearms, will bring the dumbbells towards the chest performing elbow flexion. 2 sets of 10 repetitions. Dumbbells up to 1 kg will be used.
7. Diagonal patterns exercises	Diagonal D1 flexion: participants will sit, start with shoulder extended, abducted, and internally rotated and end with shoulder flexed, adducted, and externally rotated. Diagonal D2 flexion: participants will sit, start the exercise with shoulder extended, adducted, and internally rotated and end with shoulder flexed, abducted, and externally rotated. 2 sets of 10 repetitions for each diagonal. Dumbbells up to 1 kg will be used.
8. Full can exercise	Participants will stand up, perform shoulder abduction with the elbows extended in the scapular plane, the humerus in external rotation and the thumbs pointing upwards, holding dumbbells. 2 sets of 10 repetitions. Dumbbells up to 1 kg will be used.
9. Scapular stabilization exercise	Participants will stand with shoulders flexed at 90° and hands on the wall, and will perform scapular abduction and adduction keeping hand contact with the wall and elbows extended. 2 sets of 10 repetitions.

Figure 3 - Kinesiotherapy protocol for breast cancer survivors.

Note: 1 - Stretches; 2 - Codman's pendulum exercise; 3 - Active scapular mobilization; 4 - Shoulder flexion and abduction; 5 - Shoulder elevation with dumbbells; 6 - Seated chest press with dumbbells; 7 - Diagonal patterns exercise; 8 - Full can exercise; 9 - Scapular stabilization exercise.

Sham group

SG will start intervention receiving a traditional massage, in regions different from those covered by the IG. The surface smoothing technique will be used, based on Domenico and Wood's classical massage concept.[30] Smooth, rhythmic and circular movements will be made with all the palmar surface, in order to minimize major fascial changes. Traditional massage will last 20 minutes. In the first ten minutes, the participant will stay in dorsal decubitus position and receive the technique in the abdominal region. In the last ten minutes, the participant will adopt the lateral decubitus to receive the massage in the lumbar region. After the traditional massage, the participant will perform the same kinesiotherapy protocol described above, during 20 minutes.

Sample size calculation

Sample calculation was performed using the G-Power® 3.1 software. Variable used was pain intensity in the VAS. Calculation was based on the detection of a 3-point difference between the groups.[31] Considering a power of 80% and α of 5%, we estimated 14 participants per group.

Statistical analysis

Statistical analysis will be conducted based on intention-to-treat analysis. Data will be organised in Excel® (version 2010) and then analysed in SPSS® (Statistical Package for Social Sciences, version 20.0) software. Shapiro-Wilk will be used to check the data normality. Sample characterization will be presented by descriptive statistics. To check the difference between means, the T-Student test or the U-Mann-Whitney test will be used, according to data normality. To verify treatments effects, analysis of variance (ANOVA) for repeated measurements will be used, considering two factors (two-way): time (week 1, week 4, and week 6) and group (IG and SG). Significance level adopted for all tests will be 5%.

Discussion

This study evaluated effects of MR associated with kinesiotherapy on chronic pain treatment and upper limb dysfunction in breast cancer survivors. By using stretching, strengthening and neuromuscular control exercises, kinesiotherapy has been shown to be effective, playing a central role in the rehabilitation process.[12] Whereas MR, by acting on myofascial tissue through stretching, manual pressure and sliding techniques, has shown good results in the treatment of chronic pain and upper limb dysfunctions after breast cancer surgery.[16,17,32]

It is possible that through manual therapy, stimulation of intrafascial sympathetic afferents can trigger changes in the global autonomic nervous system tone, as well as in local circulation and extracellular matrix hydration.[33] Therefore, we believe that associating a MR protocol with kinesiotherapy, we can maximize results, reducing pain and increasing functionality after breast cancer. In this way, we will be able to provide these women with a faster return to socio-labour activities, which has a positive impact on their quality of life.

In a recent systematic review with meta-analysis, it was found that manual therapy decreased the intensity of chronic musculoskeletal pain among breast cancer survivors, however, studies were scarce, with small sample size and low methodological quality.[19] Therefore, during the development of our study, we seek to reduce these gaps by describing and illustrating each of the techniques and using a simple and clear methodology. Furthermore, by adding SG, on one hand we will allow participants of both groups to have the same time of individual treatment with the therapist touch, reducing possible biases. On the other hand, therapists touch can be considered therapeutic by physical and psychological mechanisms,[34] which can make it difficult to identify a difference between groups.

Finally, chronic pain in breast cancer survivors may involve different mechanisms (nociceptive, neuropathic and/or central sensitization).[8] However, randomized clinical trials investigating chronic pain in breast cancer survivors usually do not consider pain mechanisms to address treatment.[35] By associating kinesiotherapy with MR, we can work on more than one mechanism in the same session, maximizing the results. Therefore, if the association of MR with kinesiotherapy prove to have superior effects than isolated kinesiotherapy, we can suggest that pain mechanisms might also be considered when developing a treatment programme for chronic pain of breast cancer survivors.

The study presents some limitations. Due to the proposed interventions nature, responsible therapist for implementing treatment cannot be blinded. In addition, if the intervention will be replicated in other rehabilitation centers, it should only be performed by physiotherapists with experience in MR, which eventually restricts its use. On the other hand, kinesiotherapy protocol allows for greater flexibility, as it can be adapted even for group care, enabling greater reproducibility.

Conclusion

In conclusion, the association of MR with kinesiotherapy will hopefully generate an improvement in chronic pain and functionality of breast cancer survivors. Thus, we believe that MR technique can be routinely included in clinical practice since the early stages of rehabilitation process.

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Authors' contributions

NSC, LMBS, KZ and FFS were responsible for the study conceptualization; NSC, KZ, GMS and FFS, for the methodology. NSC conducted the investigation, while FFS conducted and supervised the whole project. The original draft was written by NSC and LMBS; review and editing were performed by RS and FFS.

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Manipulation of the Fascial System Applied During Acute Inflammation of the Connective Tissue of the Thoracolumbar Region Affects Transforming Growth Factor-β1 and Interleukin-4 Levels: Experimental Study in Mice

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Fascia can become rigid and assume a fibrotic pattern due to inflammatory processes. Manipulation of the fascial system (MFS), manual technique targeting connective tissues, is commonly used in clinical practice in pain management. We aimed to verify MFS effects on the connective tissue inflammatory changes in mice. Swiss *Mus musculus* male mice (n = 44) were distributed into groups: carrageenan without treatment (Car, n = 11), carrageenan with MFS (Car + MFS, n = 12), saline without treatment (n = 10), and saline with MFS (saline + MFS, n = 11). Interleukin 4 (IL-4), IL-6, tumor necrosis factor (TNF), transforming growth factor β1 (TGF-β1), and monocyte chemoattractant protein 1 (MCP-1) levels were verified by enzyme-linked immunosorbent assay. Neutrophil (Ly-6G), macrophage (F4/80), and nitric oxide synthase 2 (NOS-2) were identified using Western blot. The MFS protocol was applied from the first to the third day after inflammation of the connective tissue of the thoracolumbar region. There was a significant MFS effect on IL-4 (p = 0.02) and TGF-β1 (p = 0.04), without increasing MCP-1, TNF, and IL-6 levels ($p > 0.05$) on thoracolumbar region from Car + MFS, in comparison with saline. Ly-6G in Car + MFS presented lower levels when compared with saline (p = 0.003) or saline + MFS (0.003). NOS-2 levels were lower in Car + MFS than in saline + MFS (p = 0.0195) or saline (p = 0.003). MFS may have an anti-inflammatory effect, based on TGF-β1 and IL-4. IL-4 may have inhibited neutrophil migration. Lower levels of NOS-2 may be linked to the lack of macrophages, which are responsible for NOS-2 expression.

Keywords: fascial system, inflammation, cytokines, mice, manipulation

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INTRODUCTION

Fascia is a connective tissue composed of collagen fibers (Willard et al., 2012) that enables sliding between surfaces (Langevin et al., 2011); it is known that it has an important role in locomotion withal, as it acts as a transmission force mechanism between adjacent synergist and antagonistic muscles (Garfin et al., 1981). It has been suggested that this transmission force mechanism occurs via collagen fibers of the connective tissue (Huijing and Baan, 2008), which shares the mechanical stress during muscle contraction (Findley et al., 2015). Moreover, the fascia resistance to pressure and traction depends on its extracellular matrix (ECM) content (Bhattacharya et al., 2010), which can be affected by inflammatory processes (Langevin et al., 2011).

Persistent inflammation processes can cause fibrosis and change mechanical properties of the connective tissue, which occurs when the main type of cells of the connective tissue, the fibroblasts (Langevin et al., 2011), proliferates (Morikawa et al., 2016) and differentiates into myofibroblasts (Morikawa et al., 2016; Pardali et al., 2017). Thereby, the stiffness of the connective tissue may affect sliding between surfaces, once the adjacent connective tissue layers are particularly relevant in structures, such as the connective tissue of the thoracolumbar region, in which the density layers correspond to aponeuroses of muscles with different traction directions: longitudinal (for latissimus dorsi, posterior serratus, and erector spinae) vs. transversal (for internal/external obliques and latissimus dorsi) (Langevin et al., 2011). If sliding between these tissues is compromised, and the fascia biomechanical properties are changed, it may contribute to musculoskeletal pain (Klingler et al., 2014).

In the early stages of acute inflammation, inflammatory macrophages type 1 (M1) are polarized by proinflammatory mediators, such as tumor necrosis factor (TNF) and interleukin 6 (IL-6), whereas in later stages, anti-inflammatory macrophages type 2 (M2) are stimulated by transforming growth factor β (TGF-β) and IL-4 (Fraternale et al., 2015). In addition, in the presence of IL-4, phagocytic cells, such as M1 macrophages, differentiate into the M2 phenotype (Mantovani et al., 2004). However, in chronic inflamed connective tissue, stiffness and fibrosis have been associated with an excess of TGF-β1 (Bouffard et al., 2008; Bove et al., 2016; Gyorfi et al., 2018) and IL-4 (Trautmann et al., 1998, 2000), as these mediators stimulate fibroblast activity (Trautmann et al., 2000) and their differentiation into myofibroblasts (Arora et al., 1999).

As a treatment for orthopedic conditions, such as stiffness and fibrosis, the manipulation of the fascial system (MFS) is commonly used (McKenney et al., 2013; Ajimsha et al., 2014). It is a manual application of a directional load (Ajimsha et al., 2014), aiming to gradually mobilize the soft tissue (McKenney et al., 2013; Rubira and Sousa, 2013) promoting mechanotransduction, mechanism by which cells convert mechanical stimuli into a chemical response (Schleip et al., 2005). The therapist is guided by the response of the patient body to determine the direction of the load and its intensity and duration (McKenney et al., 2013). The objective of the MFS is to restore optimal tension, reduce pain, and improve the myofascial complex function (Ajimsha et al., 2014).

However, MFS is poorly understood, and its effects on early inflammatory mediators of fibrotic processes have not been evaluated. In some experimental studies, such as those of Bove et al. (2016, 2019), and Altomare and Monte-Alto-Costa (2018), the effects of manual therapy in reducing tissue changes provoked by inflammation have been investigated. After the application of manual protocols, those authors have reported lower collagen type I and TGF-β1 levels in connective tissue (Bove et al., 2016), decreased neutrophils and macrophage cells and collagen deposition around the median nerve (Bove et al., 2019), lower presence of macrophages, and reduction of subcutaneous tissue stiffness (Altomare and Monte-Alto-Costa, 2018). Those studies evaluated a combination of joint mobilization and traction of skin tissue of the upper extremity in rats (Bove et al., 2016, 2019), or scar tissue mobilization (Altomare and Monte-Alto-Costa, 2018). None of those studies looked at the isolated effects of MFS on inflammatory mediators. Moreover, those studies investigated manual therapy after chronic changes in tissues. Important inflammatory mediators, such as TNF and IL-6, are present in the early phases of inflammation (Loram et al., 2007b; Annamalai and Thangam, 2017).

In the present study, using a translational research perspective, we investigated the effects of MFS on the connective tissue of the thoracolumbar in acute inflammation using a carrageenan-induced inflammation mice model. The objective of this study was to investigate the effects of MFS on inflammatory mediators and cells after induction of inflammation in the connective tissue of the thoracolumbar region with carrageenan in mice. We hypothesized that MFS would be a safe manual technique to be applied in early stages of inflammation to help inflammatory pain management in orthopedic conditions.

MATERIALS AND METHODS

This preclinical study was conducted by a partnership between Posture and Balance Laboratory at Santa Catarina State University and the Neurosciences Experimental Laboratory (LANEX) at the University of Southern of Santa Catarina (UNISUL), Brazil. The research was conducted at LANEX.

Ethics Approval

This research was approved by the Ethics Commission for the Use of Animals (CEUA-Unisul), accredited by the National Council of Animal Experimentation. The research was registered using the protocol 18.017.4.08.IV (CEUA-UNISUL). The animals were treated in accordance with the ethical principles established by the Brazilian College of Animal Experimentation and the experiments followed the ARRIVE (animal research: reporting *in vivo* experiments) (Kilkenny et al., 2010).

Abbreviations: ARRIVE, animal research: reporting *in vivo* experiments; Car, carrageenan group; ECM, extracellular matrix; IL-2, interleukin 2; IL-4, interleukin 4; IL-6, interleukin 6; IL-10, interleukin 10; iNOS, induced nitric oxide synthase; M1, macrophage type 1; M2, macrophage type 2; MCP-1, monocyte chemoattractant protein 1; MFS, manipulation of the thoracolumbar; NO, nitric oxide; NOS-2, nitric oxide synthase 2; TNF and TNF-α, tumor necrosis factor (alfa); TGF-β1, transforming growth factor β1.

Animals

Animals were bred and provided by the Federal University of Santa Catarina and reallocated at LANEX/UNISUL. This study was carried out using Swiss *Mus musculus* male mice (n = 44), weighing 45–58 g, aged 8–14 weeks. The mice were randomly distributed into four groups, as described below. Each group was housed in a polypropylene box at LANEX/UNISUL, at an average temperature of 21–23°C, under a 12/12-h light–dark cycle, having free access to water and food. The sample size was based on $n = \{[(z\ alfa + z\ beta) \times s]/sigma\}^2$ formula (Wayne and Cross, 2018) and on experimental data of our laboratory.

Groups

Animals were randomized into four groups: Carrageenan without treatment (Car, n = 11), Carrageenan treated using MFS protocol (Car + MFS; n = 12), saline without treatment (saline, n = 10), and saline treated using MFS protocol (saline + MFS, n = 11). Animals from the Car and Car + MFS groups were injected with 50 μL of carrageenan (Sigma, St. Louis, MO, United States) at 3% (diluted in saline 0.9%). Saline and saline + MFS groups were injected only with 50 μL of saline 0.9%.

Procedures

Anesthesia and Inflammation Protocols

All animals were sedated with an intraperitoneal injection of ketamine (90 mg/kg of animal weight) and xylazine (10 mg/kg of animal weight). The animals were positioned in prone position and had their back shaved with an electric shaver and Veet hair removal cream. The local needle insertion was defined as follows: two diagonal lines were drawn starting at each coxofemoral joint and ending at the lower back, at the point where the two lines intersected; a perpendicular line starting at the spine was traced; and then 1 cm was measured to the right side of the back. Thereby, the needle was inserted at an angle of 45° on the skin and projected to reach a deep layer of the connective tissue of the thoracolumbar region. The inflammation model was based on previous literature (Corey et al., 2012). The animals from the Car and Car + MFS groups were injected with 50 μL of Carrageenan (Sigma, St. Louis, MO, United States) diluted to 3% in saline 0.9%. The animals from saline and saline + MFS groups were only injected with 50 μL of saline 0.9%. The inflammation protocol has been previously trained in animal cadavers to make sure that carrageenan/saline would reach the inner layer of the connective tissue of thoracolumbar region.

The connective tissue of the thoracolumbar region was identified using the Evans blue method. A local injection of Evans blue associated with dissection was used. Careful examination revealed that three different layers could be differentiated in the lumbar region of the animals: (i) an outer layer, immediately under the skin, consisting of loose connective tissue; (ii) a middle layer, containing thick bundles of collagen fibers that run obliquely to the spine; and (iii) an inner layer, consisting of a thin sheet of parallel collagen fibers oriented perpendicularly to the spine. This revealed that traces of Evans blue were visible in the fascial layers but not in the adjacent muscles [the paravertebral (PV) muscles and gluteus muscles]. It was concluded that the injection protocol of this study reached the middle layer as well as inner layer, in contrast to the outer layer or the underlying musculature.

MFS Protocol

The Car + MFS and saline + MFS mice were treated with the MFS by a researcher blinded to the experimental protocol, a physiotherapist with 15 years of practice in manual therapy and 6 months of previous training in animal experimentation. The MFS protocol was applied at 6, 24, and 48 h after the inflammation procedure, which summed three interventions during the acute phase of inflammation, with each intervention lasting 20 min. During each MFS session, the animals in the treated groups were sedated with isoflurane at 2% and oxygen at 100% and the animals in the non-treated groups were sedated as described for 20 min but did not receive treatment to act as control groups.

The MFS protocol is illustrated in **Figure 1**. The manipulation protocol used in this study, which we had described as "myofascial reorganization" in a previous investigation (Sinhorim et al., 2019), targets the fascial system. Video recordings of the specific treatment practiced in this study were evaluated by seven international experts in manual myofascial therapy, different teaching experts in manual therapy. Based on their evaluation, the specific manual treatment used in this study can be best described as a manual connective tissue manipulation expressing a strong similarity with the Rolfing method of manual therapy (Jêdrzejewski et al., 2020). Nevertheless, it included significant modifications from the original method (which was developed for humans) and does not reflect the full depth and complexity of that method. This protocol was based on previous studies about mice anatomy and dissection of the fascial complex of mice lumbar region, with the purpose of preserving the technique objectives applied to humans, but attempting to find the most appropriate correspondence between the characteristics of human treatment when applied to mice. It was applied as follows:

> Moment 1: preparatory moment, duration of 3 min. With the animal in prone position, the physiotherapist anchored the inferior insertion of the fascial complex of the lumbar region (close to the tail) with one finger, and with other finger, the therapist performed continuous pressure for 45°, a shear load, in the superior insertion in the cranial direction (**Figure 1A**) to promote a soft stretch of connective tissue, but not a muscular one.
>
> Moment 2: straight technique, duration of 10 min. With the animal still in the prone position, the physiotherapist anchored the inferior insertion area of the connective tissue of the thoracolumbar with two fingers at the level of the animal's iliac, right and left side, and with two other fingers at the superior insertion, the therapist applied a tensile loading charge toward the back and the animal's skull (**Figure 1B**).
>
> Moment 3: diagonal technique, duration of 7 min. The animal was carefully positioned in supine position on the hands of the physiotherapist. Then, the therapist's index

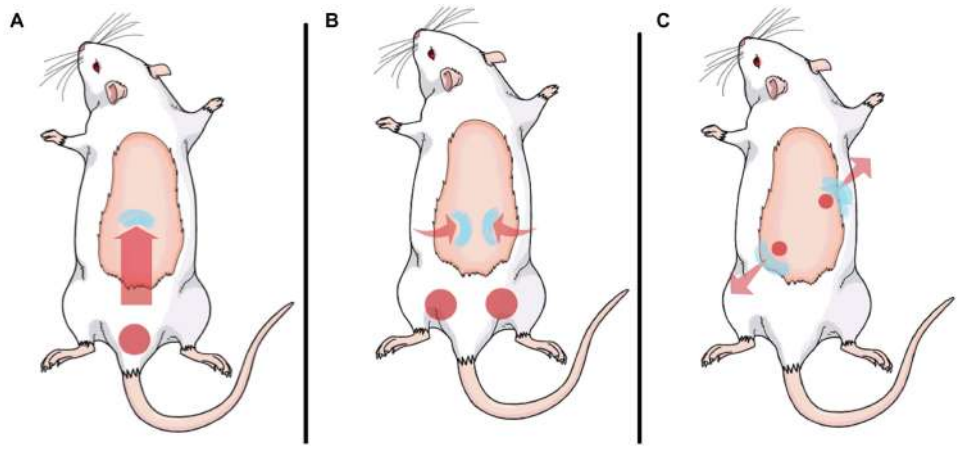

FIGURE 1 | MFS protocol was subdivided into three parts. Part 1 is represented in panel **(A)** (duration of 3 min); part 2 is represented in panel **(B)** (duration of 10 min); and part 3 is represented in panel **(C)** (total duration of 7 min, with each diagonal lasting 3.5 min).

fingers were at one side and the ring fingers at the other side of the animal's lumbar spine, in order to contemplate all the fascial complex of the lumbar region. The therapist performed a diagonal point of pressure, with a compressive load, at first with one index finger and one ring finger, and later exchanging the pressure to the other index and ring fingers, thereby forming an X on the animal's fascial complex of the lumbar region (**Figure 1C**), by that promoting a stretch of the tissue following a diagonal direction on the animal back. Each diagonal was sustained in separated moments.

The animals were euthanized at 72 h post-carrageenan/saline injection on connective tissue of the thoracolumbar region, and the tissue samples were collected.

Procedure for Collecting Tissue Samples

The animals were euthanized with an overdose of intraperitoneal anesthesia (ketamine 180 mg/kg and xylazine 20 mg/kg). The tissue samples from the connective tissue of the thoracolumbar region and underlying PV muscle and gluteus muscle of the right side of each animal were collected by dissection and stored at −80°C on a freezer for posterior analysis. The dissection was made as follows: samples were carefully detached from the underlying muscle close to the spinous processes L4–L5 using surgical scissors. The subcutaneous tissue and its three layers were included in the sample without distinction. And then, PV muscle and gluteus samples were separated from other muscles and connective tissues. Samples were stored inside 2-mL Eppendorf microtubes.

Western Blot Analysis

The samples were sprayed with a lysis buffer [100 mM Na_2VO_4, 100 mM phenylmethylsulfonyl fluoride, and a 1% protease inhibitor cocktail (P8340) (Sigma-Aldrich Co., LLC, St. Louis, MO, United States)] in T-Per (Tissue Protein Extraction Reagent; Thermo Scientific, Rockford, IL, United States). The homogenates were centrifuged at 6,000 rpm for 20 min at 4°C. The supernatant was obtained, and a separate aliquot of the protein in each sample was determined using the Bradford method (Bradford, 1976). The sample buffer [20% glycerol, 14.4 mM mercaptoethanol, 0.1% of bromophenol blue, Tris 0.2 M HCl, and 10% of sodium dodecyl sulfate (SDS)] was added at a ratio of 1:6 to the remainder of the supernatant. All the samples were boiled (95°C for 5 min) and stored at −80°C until electrophoresis analysis.

The proteins were separated using electrophoresis in a separation gel [8% acrylamide, 0.2% *bis*-acrylamide, 375 mM Tris, 0.1% SDS, 0.06% tetramethylethylenediamine (TEMED), and 0.04% ammonium persulfate] and an entry gel (4% acrylamide, 0.09% *bis*-acrylamide, 125 mM Tris, 0.1% SDS, 0.08% TEMED, and 0.03% ammonium persulfate). The samples (50 μg/well) and the molecular weight standard (Precision Plus Protein Standards, Kaleidoscope; Bio-Rad, Hercules, CA, United States) were applied to the gels, and the electrophoresis was performed at 90 V for approximately 3 h using a running buffer. After the electrophoresis, proteins were electrotransferred into polyvinylidene difluoride membranes (90 V, 90 min, and 4°C), which were blocked for 1 h at room temperature (25°C) with a 5% non-fat dry milk prepared in TBS-T (Tris-buffered saline, pH 7.4; concentration in mmol/L: 20 Tris–HCl, 137 NaCl, and 0.1% Tween 20), and incubated overnight at 4°C with primary antibodies to mouse Ly-6G, mouse F4/80, and mouse nitric oxide synthase 2 (NOS-2) at a ratio of 1:1,000 (R&D Systems Inc., Minneapolis, MN, United States), or actin–horseradish peroxidase (HRP) at a ratio of 1:50,000 (Sigma-Aldrich Co., St. Louis, MO, United States). After washing, membranes were incubated with peroxidase-conjugated secondary antibodies anti–immunoglobulin G at a ratio of 1:5,000 (Cell Signaling Technology, Danvers, MA, United States) (except for anti–actin-HRP) for 1 h at room temperature. Then, the membranes were exposed to HRP substrate (Thermo Fisher Scientific Inc., Rockford, IL, United States), and immune complexes were visualized using chemiluminescence and the

iBright CL1000 System (Thermo Fischer Scientific Inc., Rockford, IL, United States). The bands were quantified using the densitometry software from the manufacturer.

Enzyme-Linked Immunosorbent Assay

For determination of TGF-β1, TNF, IL-4, IL-6, and monocyte chemoattractant protein 1 (MCP-1) levels, a 100 μL of protein in each sample were used. These cytokine concentrations analyses were performed using the Duo Set enzyme-linked immunosorbent assay Kits (R&D Systems, Minneapolis, MN, United States) according to the manufacturer's instructions. The values obtained were estimated by interpolating data using a standard curve for each cytokine using a colorimetric assay, which was measured at 450 nm (correction at 540 nm) in a spectrophotometer (Perlong DNM-9602, Nanjing Perlove Medical Equipment Co., Nanjing, China). The values obtained were expressed in picograms per milliliter.

Statistical Analysis

The data were processed using GraphPad Prism 6 software. The Shapiro-Wilk test was applied to verify the data distribution. The data were analyzed using two-way analysis of variance (ANOVA) with Tukey *post hoc* test or using non-parametric Kruskal–Wallis with Dunn *post hoc* test, when adequate. The significance level was adjusted at 5% ($p < 0.05$), and the values were expressed as mean ± standard deviation (SD) for normal data, or median and interquartile interval for non-normal data.

RESULTS

Tissue Cytokines and Proteins in the Connective Tissue of the Thoracolumbar

In the connective tissue of the thoracolumbar region, significantly higher levels of TGF-β1 ($p = 0.047$) and IL-4 ($p = 0.026$) were found in the Car + MFS group when compared with the saline group (**Figures 2A,B**, respectively). No difference was found between groups for IL-6 ($p = 0.389$), TNF ($p = 0.555$), and MCP-1 ($p = 0.845$) (**Figures 2C–E**, respectively) (**Table 1**).

Neutrophil (Ly-6G) and Macrophage (F4/80) Membrane Proteins the Connective Tissue of the Thoracolumbar Region

There was no significant difference for the Ly-6G protein (**Figure 3A**) present on the neutrophil membrane when

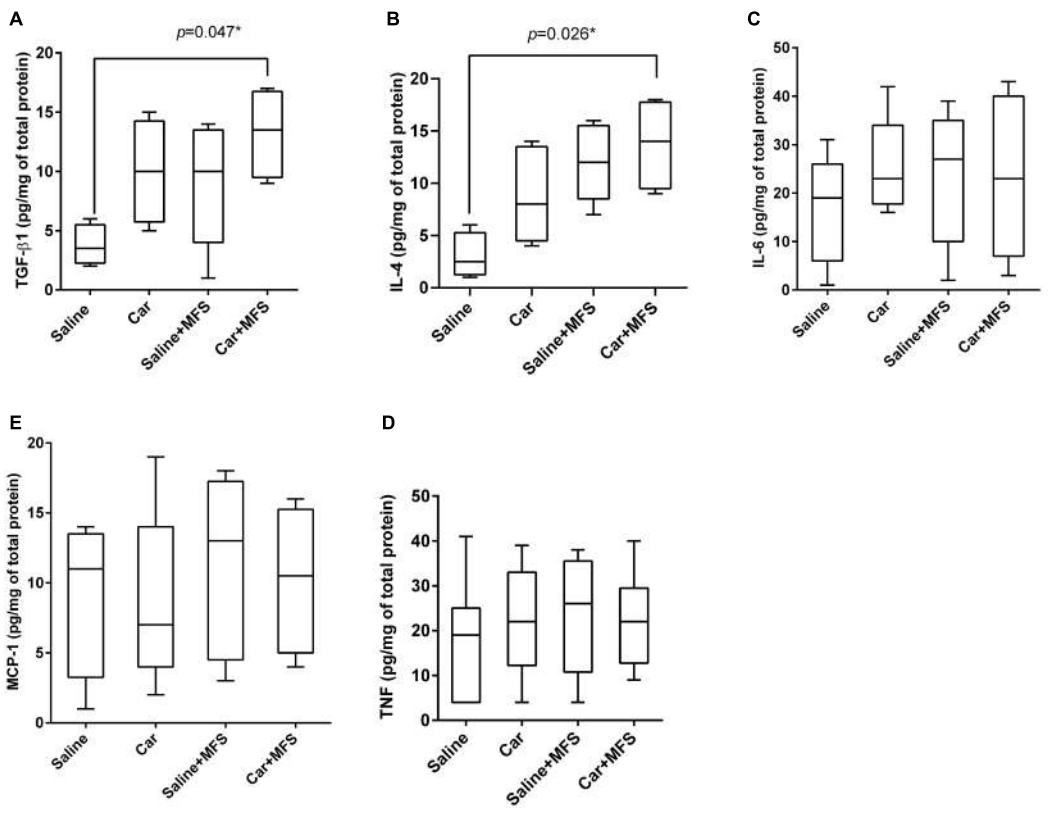

FIGURE 2 | Effect of MFS on cytokine and protein levels of mice right side TA: TGF-β1 **(A)**, IL-4 **(B)**, IL-6 **(C)**, TNF **(D)**, and MCP-1 **(E)**. Levels are represented as median (interquartile interval) by group (saline, $n = 10$; Car, $n = 11$, saline + MFS, $n = 11$, and Car + MFS, $n = 12$). Data were analyzed using the Kruskal–Wallis test, with Dunn *post hoc* test and a significance level of 5% ($p < 0.05$). *There was a significant difference between saline and Car + MFS for TGF-β1 ($p = 0.047$*) **(A)** and IL-4 ($p = 0.0265$) **(B)**.

TABLE 1 | Inflammatory mediator levels in the connective tissue of the thoracolumbar region per group.

	Saline		Car		Saline + MFS		Car + MFS		*p* values
	Median	Q3–Q1	Median	Q3–Q1	Median	Q3–Q1	Median	Q3–Q1	
TGF-β1	0.77	0.54	1.85	2.52	1.97	2.95	3.18	3.68	0.048*
TNF	0.63	4.36	0.86	2.44	1.12	2.41	0.92	2.72	0.555
IL-4	0.49	2.07	3.37	6.86	4.8	7.04	7.35	11.38	0.009**
IL-6	0.52	1.84	0.76	11.17	1.16	4.16	0.82	18.24	0.389
MCP-1	51.2	132.6	34.5	234.8	110	208.9	46.6	155.5	0.845
Ly-6G	4.42	7.12	1.23	3.40	3.89	13.61	1.62	3.62	0.437
F4/80	0.88	2.44	0.523	1.63	1.5	4.103	0.343	3.00	0.001**
NOS-2	0.95	8.02	0.3	1.65	1.18	3.612	0.293	0.65	0.002**

*Mediator levels on the connective tissues of the thoracolumbar region per group are represented by median and interquartile interval (Q3–Q1). Kruskal–Wallis with Dunn post hoc was used for statistical analysis for all variables. *There was significant ($p < 0.05$) difference for TGF-β1, IL-4, Ly-6G, and NOS-2. Differences were found between saline vs. Car + MFS (*p = 0.047) for TGF-β1; saline vs. Car + MFS (*p = 0.026) for IL-4; Car vs. saline + MFS (**p = 0.003) and saline + MFS vs. Car + MFS (*p = 0.0337) for Ly-6G; saline vs. Car + MFS (*p = 0.0337) and saline + MFS vs. Car + MFS (*p = 0.0195) for NOS-2.*

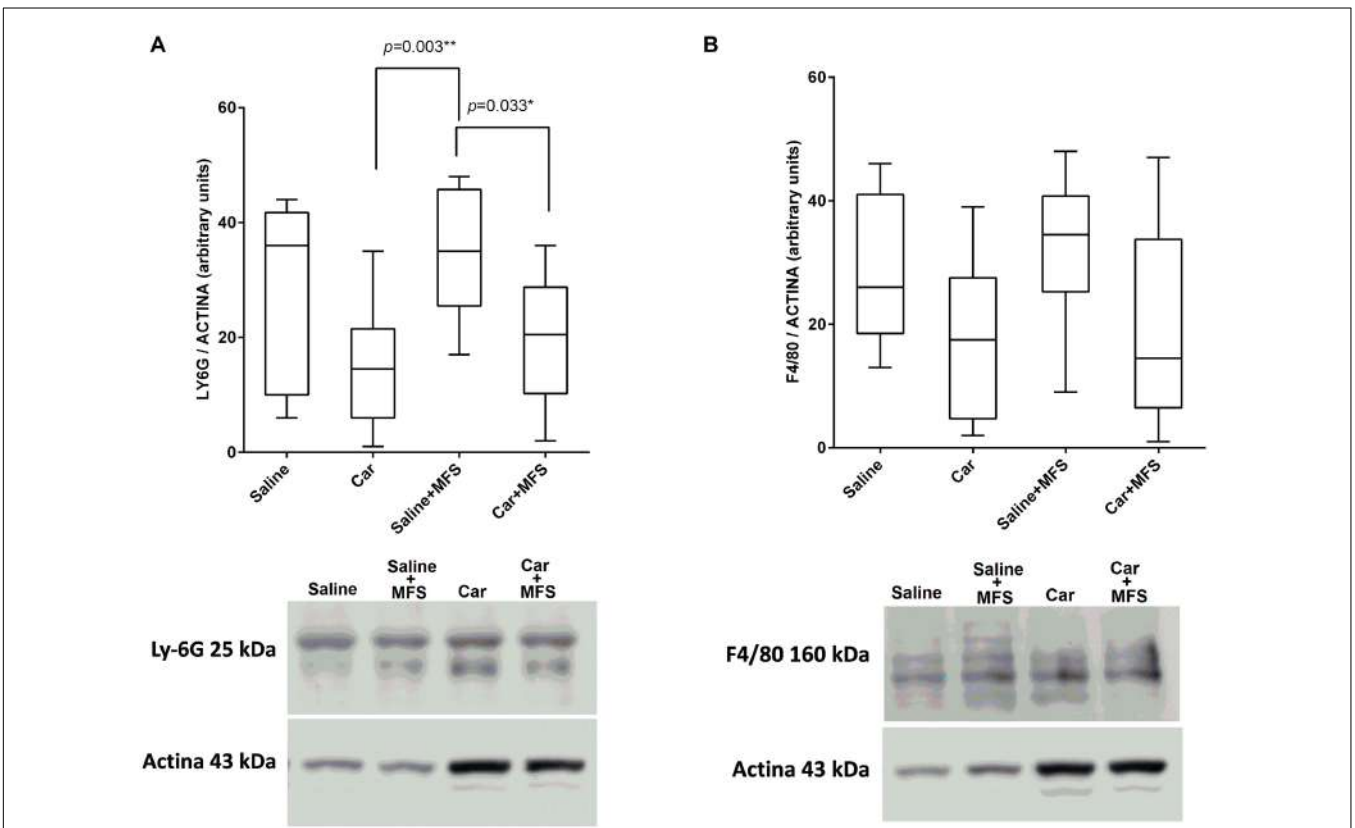

FIGURE 3 | Effect of MFS on cytokine and protein levels of the right side of TA on Ly6G **(A)** and F4/80 **(B)**. Levels are represented as median (interquartile interval) by group (saline, $n = 10$; Car, $n = 11$, saline + MFS, $n = 11$, and Car + MFS, $n = 12$). Data were analyzed using the Kruskal–Wallis test, with Dunn *post hoc* test and a significance level of 5% ($p < 0.05$). *There was a significant difference between the Car and saline + MFS groups ($p = 0.0033$**) and between the saline + MFS and Car + MFS groups ($p = 0.0337$*) for Ly-6G protein **(A)**. No difference was found between treated and non-treated animals on terms of F4/80.

comparing the saline with the Car group ($p = 0.086$), the saline with saline + MFS group ($p > 0.999$), the saline with the Car + MFS group ($p = 466$), and/or the Car with the Car + MFS group ($p > 0.999$). Interestingly, Ly-6G protein levels were significantly lower in the Car + MFS when compared to saline ($p = 0.003$) or saline + MFS ($p = 0.033$) groups. No difference was found for the F4/80 protein presented on the macrophage membrane when comparing the saline and Car groups ($p = 0.437$), the saline and saline + MFS groups ($p > 0.999$), the saline and Car + MFS groups ($p = 0.652$), the Car and Car + MFS groups ($p > 0.999$), or the saline + MFS and Car + MFS groups ($p = 0.105$) (**Figure 3B**).

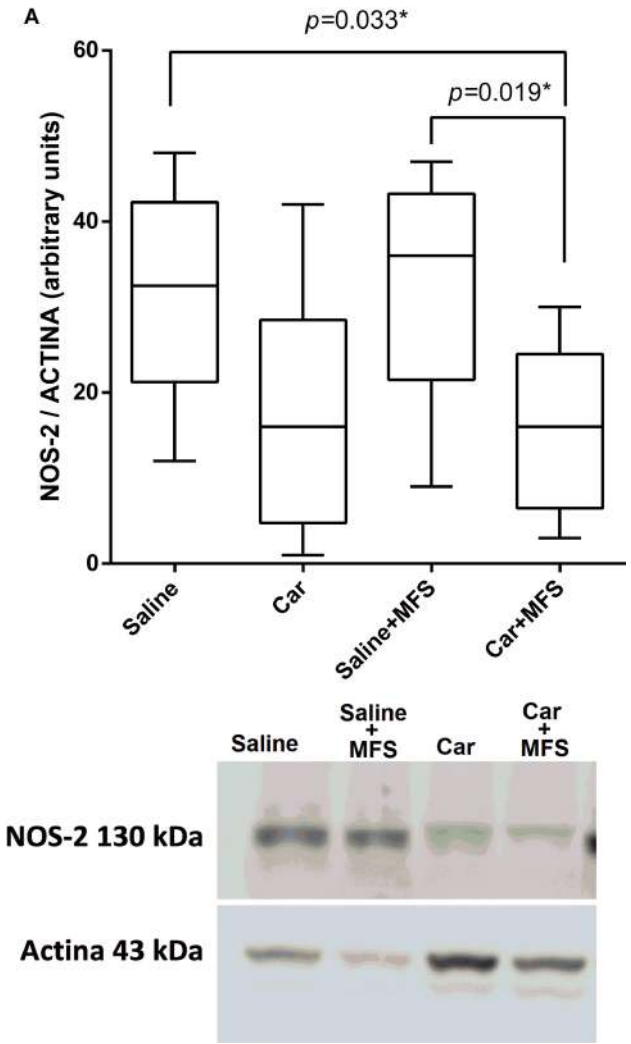

FIGURE 4 | Effect of MFS on NOS-2 levels in the right side of the TA. Levels are represented as median (interquartile interval) by group (saline, $n = 10$; Car, $n = 11$; saline + MFS, $n = 11$; and Car + MFS, $n = 12$). Data were analyzed using the Kruskal–Wallis test, with Dunn *post hoc* test and a significance level of 5% ($p < 0.05$). *There was a significant difference between the saline and Car + MFS ($p = 0.0337$*) and Car groups ($p < 0.0033$) and between the saline + MFS and Car + MFS groups (0.0195*).

NOS-2 on the Connective Tissue of the Thoracolumbar Region

As shown by Western blot analysis, NOS-2 levels (**Figure 4**), the enzyme responsible for the synthesis of nitric oxide (NO), were not different between the saline and Car groups ($p = 0.093$), the saline and saline + MFS groups ($p > 0.999$), the Car and Car + MFS groups ($p > 0.999$), or the Car and saline + MFS groups ($p > 0.056$). The levels of NOS-2 were significantly lower in the Car + MFS group when compared with the saline ($p = 0.033$) and the saline + MFS ($p = 0.019$) groups.

Tissue Cytokines in PV and Gluteus Muscles

In the PV muscle, there was no difference in the levels of TGF-β1 ($p = 0.167$) (**Figure 5A**), IL-4 ($p = 0.124$) (**Figure 5B**), IL-6 (**Figure 5C**) ($p = 0.480$), TNF ($p = 0.144$) (**Figure 5D**), or MCP-1 ($p = 0.686$) (**Figure 5E**) between groups ($p > 0.05$) (**Table 2**). In the right gluteus muscle, no difference was found between groups for TGF-β1 ($p = 0.632$) (**Figure 5F**), IL-6 ($p = 0.485$) (**Figure 5G**), or TNF ($p = 0.375$) (**Figure 5H**) (**Table 3**).

DISCUSSION

Significantly higher levels of TGF-β1 and IL-4 were found in the connective tissue of the thoracolumbar region in the animals with inflamed tissue and subsequently treated with MFS when compared with the group of animals administered with saline. The levels of Ly-6G protein and NOS-2 were significantly lower in the inflamed and treated with MFS group rather than in the saline group.

The excess of TGF-β1 has been associated with fibrosis formation in several models of treatment of chronic inflammation (Bouffard et al., 2008; Bove et al., 2016; Gyorfi et al., 2018), as it has been for IL-4 (Trautmann et al., 1998, 2000). In models of chronic inflammation, different manual therapies, such as joint mobilization and upper extremity skin traction (Bove et al., 2016, 2019), tissue stretching *ex vivo* (Bouffard et al., 2008) and mobilization of the fibrotic scar (Altomare and Monte-Alto-Costa, 2018) are related to a positive improvement of this fibrotic change in the connective tissue. Among the positive changes, lower deposition of type I collagen and TGF-β1 in connective tissue (Bouffard et al., 2008; Bove et al., 2016), lower deposition of collagen and fewer presence of neutrophils and macrophage around median nerve (Bove et al., 2019), improvement of skin mobility, and reduction of ECM stiffness (Altomare and Monte-Alto-Costa, 2018) have been observed.

However, during acute inflammation, the finding of an elevation in the levels of TGF-β1 together with IL-4 was not expected. Yet we observed the enhancement of these two mediators without elevating the levels of proinflammatory cytokines, such as TNF and IL-6 in the connective tissue of the thoracolumbar region. In this way, the TGF-β1 together with IL-4 may be acting as proresolving cytokines. This enhancement could be related to an effect of MFS on the connective tissue, and it could be associated with proresolutive environment, which was promoted by the mechanical stimulation.

Berrueta et al. (2016) suggested that mechanical stimulation has an effect on inflammation resolution in connective tissue. In their study, a mechanical stimulus induced by a stretching had promoted a proresolutive environment in a rat model (Berrueta et al., 2016). The *in vivo* results showed fewer neutrophil cells and a widespread increase in proresolving mediators such as RvD1 and RvD2 in the stretched rats compared with the non-stretched (Berrueta et al., 2016).

By using a similar approach (stretching a connective tissue) in a breast cancer mice model (Berrueta et al., 2018), a daily

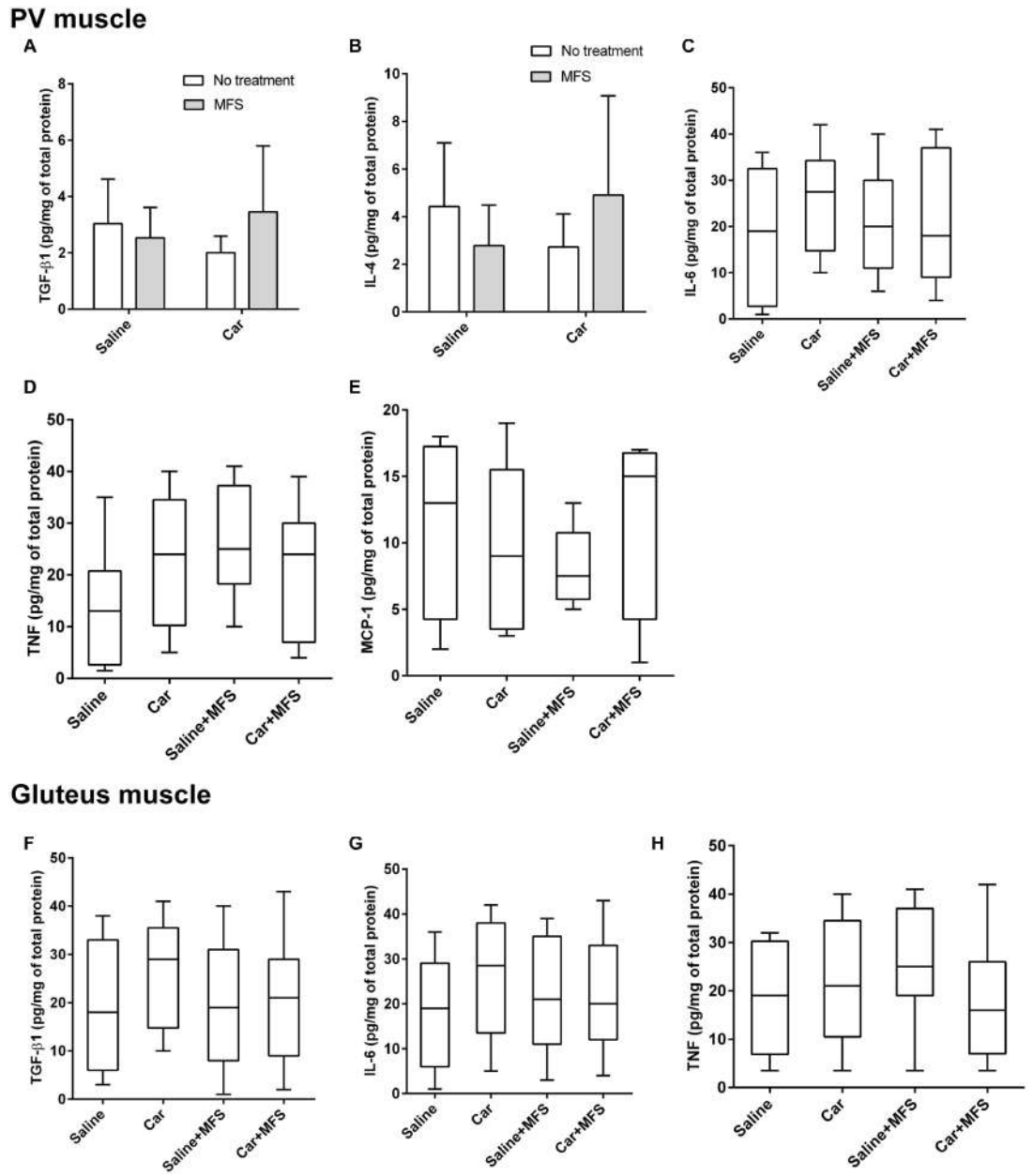

FIGURE 5 | No significant difference was found in the protein and cytokine levels of PV and gluteus muscles. TGF-β1 **(A)**, IL-4 **(B)**, IL-6 **(C)** TNF **(D)**, and MCP-1 **(E)** are representative of the PV of saline (n = 10), saline + MFS (n = 11), Car (n = 11), and Car + MFS (n = 12). TGF-β1 **(A)** and IL-4 **(B)** are represented as mean ± SD and were analyzed using ANOVA with Tukey *post hoc* test. IL-6 **(C)**, TNF **(D)**, and MCP-1 **(E)** are presented as median (interquartile interval) and were analyzed using Kruskal–Wallis with Dunn *post hoc* test. Gluteus TGF-β1 **(F)**, IL-6 **(G)**, and TNF **(H)** of saline (n = 10), saline + MFS (n = 11), Car (n = 11), and Car + MFS (n = 12) are shown as medians (interquartile intervals) and were analyzed using Kruskal–Wallis with Dunn *post hoc* test. On the PV muscle, there was no difference between groups for TGF-β1 ($p > 0.1673$) **(A)**, IL-4 ($p > 0.1241$) **(B)**, IL-6 ($p > 0.7023$) **(C)**, TNF ($p > 0.1437$) **(D)**, and MCP-1 ($p = 0.68$) **(E)** levels. In the right gluteus muscle, no difference was found between groups for the TGF-β1 ($p = 0.6329$) **(F)**, IL-6 ($p = 0.48$) **(G)**, or TNF ($p = 0.3750$) **(H)**.

gentle stretching for 10 min for 4 weeks led to significantly slow tumor growth and a 52% smaller tumor size in the stretched mice compared with the non-stretched mice; that said, the reduction in the tumor could be associated with the cytokine levels, according to the authors. They did not observe individual group differences but reported that IL-10, IL-2, IL-6, TNF-α, and interferon γ were up-regulated in the stretch group. The tumor levels of lipid-derived specialized proresolution mediators, RvD1 and RvD2, which promote the natural resolution of inflammation, were significantly greater in the stretched compared to the non-stretched mice (Berrueta et al., 2018). In contrast to their results, we did not observe up-regulation of TNF-α or IL-6,

TABLE 2 | Inflammatory mediator levels in PV muscle per group.

	Saline		Car		Saline + MFS		Car + MFS		*p* values
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	
TGF-β1	3.03	±1.59	2.00	±0.59	2.53	±1.08	3.45	±2.35	0.167
IL-4	4.43	±1.39	2.72	±1.39	2.78	±1.70	4.91	±4.17	0.124
	Median	Q3–Q1	Median	Q3–Q1	Median	Q3–Q1		Q3–Q1	*p* values
TNF	0.99	5.74	2.41	7.45	2.47	8.579	2.44	7.43	0.144
IL-6	1.84	3.82	3.03	9.21	2	5.755	1.77	8.86	0.480
MCP-1	33.4	111.1	23.1	216	20.5	18.1	46	50	0.686

Mediator levels on PV muscle per group are represented. TNF, IL-6, and MCP-1 levels were analyzed using Kruskal–Wallis with Dunn post hoc test and are represented by median and interquartile interval (Q3–Q1). TGF-β1 and IL-4 were analyzed using ANOVA with Tukey post hoc test and are represented by mean and SD. No significant differences were found between groups for all variables.

TABLE 3 | Inflammatory mediator levels in gluteus muscle per group.

	Saline		Car		Saline + MFS		Car + MFS		*p* values
	Median	**Q3–Q1**	**Median**	**Q3–Q1**	**Median**	**Q3–Q1**	**Median**	**Q3–Q1**	
TGF	1.45	8.65	3.51	12.09	1.51	11.58	1.82	18.89	0.632
TNF	1.09	3.49	1.47	15.8	1.89	37.3	0.794	47.6	0.375
IL-6	0.88	3.57	2.06	6.99	1.26	4.55	0.997	7.99	0.485

Mediator levels on gluteus muscle per group are represented by median and interquartile interval (Q3–Q1). Kruskal–Wallis with Dunn post hoc was used for statistical analysis for all variables. No differences were found between groups.

although in both studies (Berrueta et al., 2016, 2018) manual therapy was not applied as treatment as well done in our study. Our findings may be also related to a proresolutive state facilitated by mechanical stimulation of the connective tissue during acute inflammation.

The enhancement of IL-4 and TGF-β may favor the recruitment of macrophage type 2 (M2), an anti-inflammatory macrophage phenotype. In skeletal muscle, during the first postinjury hours, there is a recruitment of circulating monocytes, which can enter the tissue and differentiate into inflammatory macrophages type 1 (M1). At the time the M1 macrophages are exposed to an inflammatory environment and perform the muscle fiber debris phagocytosis, they are switching into the M2 profile, and when they are stimulated by IL-4, these M2 (anti-inflammatory) macrophages start to produce TGF-β1 (Arnold et al., 2007). These anti-inflammatory macrophages (M2) are stimulated in the presence of mediators such as IL-4 and TGF-β (Fraternale et al., 2015; Sang et al., 2015), whereas M1 macrophages are polarized by TNF and IL-6. Additionally, IL-4 is associated with the transformation of M1 into M2 macrophages (Mantovani et al., 2004). Moreover, it may be possible that TGF-β1 and IL-4 interact with one another to provide a proresolutive environment, once the increasing concentration of the combination of TGF-β1 and IL-4 diminishes the production of other ILs, including IL-4 as demonstrated by Dardalhon et al. (2008).

Although we observed an increase in TGF-β1 and IL-4 at 72 h after inflammation, there was no significant increase in MCP-1 or F4/80 protein in the connective tissue of the thoracolumbar region. It is presumed that the massive presence of F4/80$^+$ cells occurs from the fourth day onward, as observed by Brigitte et al. (2010). In this way, it is possible that F4/80$^+$ cells would be detectable only after that period. It has been shown that in the carrageenan inflammation model, the presence of mononucleated cells, such as macrophages, starts after 48 h (Martin et al., 1994). Brigitte et al. (2010) did not use carrageenan, but notexin, and they observed a peak of monocyte/macrophage cells (F4/80$^+$ cells) on the epimysium on the fourth day after inflammation. These cells remained elevated in number until the 12th day on the epimysium/perimysium of the tibial and PV muscles of rats (Brigitte et al., 2010).

There was significant decrease in Ly-6G expression in the Car + MFS group when compared to the saline + MFS, as there was significant decrease in its expression in Car + MFS group when compared with saline group. There was no difference between the Car and the Car + MFS group. The animals that received carrageenan injection treated with MFS showed higher levels of IL-4, which inhibits chemotaxis and migration of neutrophils (Saleem et al., 1998; Impellizzieri et al., 2019) to the point that systemic inhibition of IL-4 increases the influx of CD11b$^+$Ly6G$^+$ cells (neutrophils) during infection (Woytschak et al., 2016). We observed lower levels of Ly6G in the Car and the Car + MFS groups, but this finding could be related to the enhancement of IL-4. There was no significant difference between the saline + MFS and the Car groups for IL-4, whereas there was difference between the saline + MFS and the Car groups for Ly6G.

Lower levels of Ly6G$^+$ cells could be explained by NOS-2 [induced NOS (iNOS)] reduction, as Salvemini et al. (1996) demonstrated that iNOS inhibition also attenuates neutrophil infiltration during carrageenan inflammation of a paw in a mouse model. Our findings differ from those of Salvemini et al., as there

was significant difference between the saline and the Car + MFS groups for Ly6G, but not for NOS-2, thereby the presence of a few neutrophils could be linked to the lack of macrophages, according to Rigamonti et al. (2013), in acute muscle injury. Although, iNOS is produced early by neutrophils, by day 3 after induction of inflammation, iNOS is produced by macrophages. We evaluated those NOS-2 levels at the third day.

Salvemini et al. (1996) identified that neutrophils were not the only source of iNOS, as macrophage-like cells also expressed the enzyme at their membranes. The expression of iNOS was detected at 6 h after paw inflammation in the carrageenan mice model, and the maximal expression of iNOS occurred at 10 h after inflammation. Immunoreactivity for iNOS was detected in macrophage-like cells, but not in neutrophils, which suggests that resident macrophages or infiltrated monocytes can be a source of NO as produced by iNOS (Salvemini et al., 1996); however, our data did not show an increase in F4/80 protein (macrophages). In addition, the monocytes derived from the blood have shown their peak on connective tissue around the muscle connective tissue (epimysium/perimysium) by the fourth day after inflammation (Brigitte et al., 2010); this period did not coincide with the period evaluated in our study. Under these circumstances, it is not likely that MFS has a direct or little effect on iNOS levels.

It is to be noted that iNOS inhibition, as shown by Liu et al. (2015), on the fourth day of rats inflamed with notexin and treated with an inhibitor of iNOS, provoked a major infiltration of $F4/80^+$ cells when compared to the group inflamed/without inhibitor agent. Liu et al. (2015) concluded that NO augments mRNA expression of TGF-β1 and IL-10 and decreases MCP-1, TNF, IL-6, and proinflammatory cytokines. In our study, there was an increase in TGF-β1 without significant changes in the $F4/80^+$ levels on the third day after inflammation. In addition, there was no significant change in MCP-1 between groups. The TGF-β1 levels may have suffered some effect from MFS while inflammatory cells may have not.

Another important fact to be noted is that MFS did not cause an increase or spread of inflammation provoked by carrageenan, as there was no significant increase of proinflammatory mediators (TNF and IL-6) at 72 h after carrageenan injection. This agent alone increased TNF and IL-6 levels in the first hour after inflammation when compared with the saline group (Loram et al., 2007b; Annamalai and Thangam, 2017). However, in this model, TNF and IL-6 levels were not different at 24 h between rodents injected with saline or carrageenan (Loram et al., 2007a,b). In addition, a lack of TGF-β1, IL-4, MCP-1, TNF, or IL-6 in the underlying paraspinal muscles or gluteus in either treated or untreated animals suggests that the MFS protocol does not cause spread of proinflammatory factors to the surrounding tissue.

It is to be noted that no differences were found between groups for ILs and inflammatory mediators, including IL-4 and TGF-β1, on underlying muscles, as MFS is specifically applied on the connective tissue of the thoracolumbar. Therefore, MFS may be safe to be applied in the management of early stages of acute inflammation in orthopedic conditions, as it may have a proresolutive effect on inflamed tissue without significant recruitment of inflammatory cells or enhancement of proinflammatory mediators.

In conclusion, there may be a potentiating effect on the production of TGF-β1 and IL-4, anti-inflammatory factors, without increasing MCP-1, TNF, and IL-6 proinflammatory factors in carrageenan model. MFS had no direct effect on $Ly6G^+$ or $F4/80^+$ cells, whereas $Ly6G^+$ may have little or no association with IL-4 raising. NOS-2 reduction may be linked to the lack of increase in $F4/80^+$ cells, which can be major producers of NOS-2 and are not yet present in the tissue at the third day in a significant amount. Also, there were no significant differences between treatment and control (saline) animals for F4/80. Therefore, NOS-2 reduction is not likely to be related to the MFS protocol. In addition, there were no significant changes in TGF-β1, IL-4, MCP-1, TNF, and IL-6 in underlying muscles. The lack of TGF-β1, IL-4, MCP-1, TNF, or IL-6 into the underlying paraspinal muscles in either treated or untreated animals suggests that the MFS protocol does not cause spread of proinflammatory factors to the surrounding tissue. MFS specifically targets the connective tissue, but further investigation is needed to observe the effects of this technique in early phases and later phases of inflammation of the connective tissue. We conclude that MFS may be a safe treatment to help manage acute inflammatory processes in orthopedic pain conditions, as it does not provoke enhancement of inflammation, but it promotes a proresolutive environment on treated connective tissue.

The differences in the function and local topographical anatomy of the thoracolumbar fascia of rats and mice to that of humans should be taken into account, because of their differences in locomotion, basic anatomy, and posture (Loram et al., 2007a). However, previous examinations by other investigations with fascial tissues from different types of mammals have revealed common adaptive physiological responses of such connective tissues in response to mechanical stimulation (Cao et al., 2015; Langevin et al., 2018; Paxton et al., 2020). It is therefore suggested that the basic findings about these physiological responses from the present study will most likely also apply to some degree to the mechanoadaptive response of the connective tissue of the thoracolumbar region of human.

LIMITATIONS

As it is an unprecedented study, some aspects may have influenced its results: sample collection was performed at 72 h (3 days) after inflammation; during this period, a transition phase may have occurred, and an increase in inflammation preceding a chronic stage may have occurred in this model. Further research with a carrageenan model must consider the experiments using a time-course design, where carrageenan inflammation effects alone can be evaluated at 6, 24, 48, 72 h, and after the fourth day, in a way of identifying the cell and mediator profiles of this model. The detailed profile of carrageenan inflammation following both acute and chronic stages is not well established in the literature. After that, an MFS treatment using this model is suggested to be applied in the first 4 days, to compare with no MFS treatment conditions. Anesthesia with ketamine may have influenced

the results, but it was chosen to avoid pain avoidance reactions by the animals; however, the substitution of ketamine by isoflurane has been suggested. However, ketamine this influence may have been minimal, as observed by Goulart et al. (2005). The author did not report any collateral effects or influence by anesthesia using ketamine and xylazine when investigating carrageenan inflammation effects in the temporomandibular joint of rats.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The animal study was reviewed and approved by Ethics Committee for the Use of Animals – University of the South of Santa Catarina.

AUTHOR CONTRIBUTIONS

MF and LS: literature review, data collection, data analysis, and final edition. DM and RS: final edition. NM-P and GS: data collection. VH: data collection, data analysis, and final edition. GS: data analysis and final edition. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer JD declared a past co-authorship with one of the authors RS to the handling editor.

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Myofascial release strategies and technique recommendations for athletic performance: A systematic review

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ABSTRACT

Objective: To identify the effects of instrument-assisted soft tissue mobilization (IASTM) and foam roller self-myofascial release (FRSMR) strategies and verify their results in athletic performance.
Method: Systematic review conducted in four databases from 2017. The inclusion criteria were randomized controlled trials assessing the effects of two forms of soft tissue mobilization on athletes' performance. The risk of bias was analyzed using the Cochrane Handbook scale.
Results: Ten studies were included for qualitative analysis. IASTM increased range of motion, knee joint kinetic force, peak torque, and angular velocity in dorsiflexion and plantar flexion. The technique increases isometric strength and isokinetic power in vertical jumping. FRSMR was relevant in counter movement jumping between the pre- and post-intervention conditions, mainly by increasing strength in the initial jumping phase.
Conclusions: IASTM should be used in sports preparation to improve muscle response and explosive force production. FRSMR increases flexibility as it tends to restore tissue elasticity, but it does not improve aerobic activity. The suggested time for strategy intervention is at least 90 s per muscle group.

1. Introduction

The fascial system is a three-dimensional matrix of connective tissue that covers the entire body, including muscles, ligaments, tendons, joint capsules, retinacula, and other fibrous tissues. It can be defined as an elastic unbroken tensional network used to store kinetic energy (Bond et al., 2019).

In healthy tissue, Fascia can assist with workloads beyond the muscle's ability to contract due to its elastic quality. Data from other studies suggest that the manipulation of this system can increase joint range of motion (ROM) and the recovery process, decreasing the effects of acute muscle soreness, delayed onset muscle soreness, and post-exercise muscle performance (Bond et al., 2019; Healey et al., 2014; Sullivan et al., 2013). The Fascia is essential to share mechanical stress during muscle contraction and to transmit force between antagonistic and synergistic muscles, probably via collagen fibers and fibrous expansions and the intermuscular septum, with possible participation in the pain regulation endocannabinoid system (Fede et al., 2020; Findley et al., 2015; Stecco and Day, 2010).

During the 2010s, studies investigated the effectiveness of several soft tissue manipulation (STM) therapies, such as trigger point therapy, active release, and self-myofascial release (SMR), in increasing joint ROM and muscle strength (Bond et al., 2019; Healey et al., 2014; Santa Cruz et al., 2017; Schroeder and Best, 2015). Myofascial interventions were not different from control groups for strength muscle gains (Bond et al., 2019), jump performances and muscle soreness (Healey et al., 2014), as reported in previous literature riveiw (Mauntel et al., 2014). However, signifincatly gains in flexibility post compared to pre self myofascial release intervention have been reported in previous literature (Santa Cruz et al., 2017; Schroeder and Best, 2015).

Clinicaly, instrumented myofascial release may be usefull to apply, as they may indirectly improve exercise performance in athltetes and during return to sport rehabilitation, by improving joint ROM (Schroeder and Best, 2015). In sports, SMR has become a potential

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self-administered intervention used in rehabilitation and physical conditioning processes (Grieve et al., 2015).

Other techniques include actions to release the muscle fascia, such as instrument-assisted soft tissue mobilization (IASTM), foam roller self-myofascial release (FRSMR), and several other types of massage rollers such as bars and sticks (Wiewelhove et al., 2019). However, despite being popular, their physiological effects are still not well elucidated in the scientific literature, and there is no consensus on the ideal program to improve athletic ROM, recovery, and performance (Grieve et al., 2015).

Some STM techniques have been ineffective, such as pre-rolling for warming up or post-rolling to improve recovery, as reported by Wiewelhove et al. (2019). The authors reported that pre-rolling showed little improvement in sprint performance and flexibility but no effect on jumping and muscle strength. On the other hand, post-rolling slightly attenuated exercise-induced sprint performance and muscle strength declines (Wiewelhove et al., 2019).

Other techniques were not convincing, probably because the implementation of different strategies, such as effleurage, petrissage, pinching, wringing, tapotement, vibration/shaking, friction, and compressions, did not specifically affect or reach the fascial system (Davis et al., 2020). In addition, there was no evidence of significant effects of these techniques on jump performance, muscle strength, sprint, and endurance (Davis et al., 2020).

As for sports performance conditions, the conception involves recognizing power mediators and analytical conceptions (Turpin and Watier, 2020). Better sports performance demands much more than just checking the number of segments involved in movement but understanding the complex combination of mechanical factors involving the musculature and the central nervous system (CNS) limitations (Blake et al., 2012; Turpin and Watier, 2020).

Thus, a more intrinsic analysis with contemporary data is necessary to evaluate and synthesize evidence to better prepare the athlete since some specific strategies, such as pre-rolling, pointed to a greater effect on ROM than passive action (Cheatham et al., 2015).

Although the published literature shows some results regarding STM and myofascial release (Bond et al., 2019; Wiewelhove et al., 2019), IASTM and FRSMR are poorly understood regarding their biomechanical characteristics and myofascial system particularities. Therefore, verifying the practical characteristics and specific coefficients that favor sports performance is necessary. This study aims to identify the effects of the IASTM and FRSMR strategies and verify whether they are favorable predictors for improved athletic performance.

2. Methods

2.1. Inclusion and exclusion criteria

This review was submitted at PROSPERO under the register CRD42023400014. The inclusion criteria were randomized and crossover randomized clinical trials published from 2017 to June 2022 (last 5 years) in Portuguese, English, and Spanish. Studies inclusion sample criteria should clearly state: people aged from 16 to 45 years, and the specific term “athlete” should be mentioned as the study sample inclusion criteria, or the following terms: “team [sport] player” (of any kind of team sports), active subjects reporting sport practice and the word “sport” should be mentioned; “[sport] students”, high school [sport] team player or College [sport] team player. The literature search started in April 2022 and ended in June 2022. The exclusion criteria were studies with techniques not related to myofascial manipulations, with participants aged under 16 years or including as sample: (a) “untrained”; (b) “sedentary”; (c) “regularly active participants” without mentioning any sport, any sport training of any level, or the specific word “athlete”; (d) “physically active participants” without mentioning any sport practice, any sport training of any level, or the specific word “athlete”. Personal opinions, observational studies, laboratory studies, editorials, comments, letters, booklets, newspapers, and conference abstracts were excluded as well.

Outcomes included the physiological and biomechanical aspects of an athlete’s best performance in sport specific ou functional tests related to sport practice after myofascial release strategies, with systematic and statistical data based on results already established in the scientific literature.

2.2. Information sources

The study used Health Sciences Descriptors from the Latin American and Caribbean Health Sciences Literature (LILACS) Virtual Health Library to obtain keywords from the Scopus, PubMed/MEDLINE, LILACS, SPORTDiscus, and Embase databases.

2.3. Search strategy

The descriptor search and data collection were conducted in April 2022. The following descriptors were selected: *musculoskeletal manipulations, fascia, athletic performance,* and *tissue adhesions* with the Boolean operator “OR.” The same search strategy was used in all databases: *“Musculoskeletal manipulations” OR “Fascia” OR “Athletic Performance” OR “Tissue Adhesions;” “Fascia” OR “Athletic Performance” OR “Tissue Adhesions” OR “Musculoskeletal manipulations;” “Athletic Performance” OR “Tissue Adhesions” OR “Musculoskeletal manipulations” OR “Fascia;” “Tissue Adhesions” OR “Musculoskeletal manipulations” OR “Fascia” OR “Athletic Performance.”*

The search for eligible studies was based on the PICO strategy (Santos et al., 2007) mediated by the question “What is the effect of myofascial release on athletes’ performance?” Thus, the population of interest included athletes; the intervention included myofascial release, connective/connective tissue therapy, or instrument-assisted or manual soft tissue mobilization (combined or alone); the comparison included placebo, sham, or control. Athletic or sports performance tests were considered the primary outcome; secondary outcomes were pain, flexibility, stiffness, ROM, and aerobic activity. Table 1 describes the general characteristics of the included the studies and the respective strategies used.

2.4. Selection process

A systematic literature review was developed using a flow diagram (Fig. 1) based on the PRISMA - 2020 checklist (Page et al., 2021). The protocol included an evaluation report.

2.5. Data collection process and list

After the initial selection in the chosen databases according to the inclusion criteria, a reference selection process for systematic reviews included the following steps: identification of repeated studies, descriptor reading, title reading, abstract reading, and methodological analysis. The exclusion criteria were studies not related to the use of SMR strategies, different populations, methods, and results not elucidated between strategies and performance-related factors.

The studies included physiological aspects, the techniques and methods used by the researchers, and statistical analyses. This collection process was organized as follows: three authors collected information about the selected articles, such as authors and year of publication, place of data collection, type of study, number of participants, sample number, treatment period, and factors related to IASTM and FRSMR and athletic performance before and after intervention, and aspects related to pain, flexibility, stiffness, ROM, and excess classification criteria. After compiling the studies’ data and results, they were verified by a fourth author who organized the findings of the selected articles. A fifth reviewer clarified possible divergences using the pre-protocol to make choices.

Table 1
General characteristics of the studies selected in qualitative synthesis.

First Author/ Year/ Country	Sample/ Genre/ Type of study	Time (Min/ number of sessions)	EG	CG	Intervention and outcome variables
Blades et al., (2022) (UK)	Boxing athletes (n = 11, M; CRCT)	FR_{30s} (4 min) FR_{60s} (8 min)	FR_{30s} = 11 FR_{60s} = 11	CG (n = 11)	Outcome variables: measurements immediately after and 15 min post-intervention: ankle dorsiflexion ROM (distance from the wall), flexibility (sit and reach; cm), and CMJ and SJ height.
Camargo et al., (2021) (Brazil)	Cycling athletes (n = 10, M; CRCT)	5 min (1 min for each group)	FR (n = 10)	CG (n = 10)	FRSMR on the vastus lateralis and rectus femoris, hamstrings, tibialis anterior, and gastrocnemius. Outcome variables: mean and maximal power (W) in the 3-min all-out test; pressure pain threshold (kgf) on the rectus femoris and vastus lateralis, perceived exertion (BORG-10 scale), and the pleasure/ displeasure scale.
Giovanelli et al., (2018) (Turkey)	Mountain running, parkour athletes (n = 13, sex not reported; RCT)	8 min (1 min for each group)	FR (n = 7)	CG (n = 6)	FRSMR on the plantar fascia, anterior and posterior thigh and leg. Velocity and Energy Expenditure (VO_{2max}); Vertical SJ and CMJ power.
Hsu et al., 2021 (China)	Elite table tennis athletes (n = 23, M/F = 14/9; RCT)	8 min of dynamic stretching combined with 12 min of intervention	DS + VFR (n = 23) DS + FR (n = 23)	SS (n = 23)	Intervention (DS + FR or DS + VFR) on the calcaneus, hamstrings, hip flexors, quadriceps femoris, erector spinae, and rotator cuff. Outcome variables: flexibility (sit and reach), standing broad jump test distance, sitting medicine ball throwing test, and Edgren's side step test.
Kim and Yim (2018) (Korea)	Soccer athletes (n = 40, M; RCT)	60 min, 5x/ week, 12 weeks	IASTM (n = 20)	CG (n = 20)	Rehabilitation exercise combined with IASTM. Outcome variables: Knee isokinetic power (extension and flexion) at 60°/ s and 180°/s and ankle isokinetic power (dorsiflexion and plantar) at 30°/s and 120°/s; muscle fatigue in the dominant limb at 60°/s; flexibility (sit and reach), side step (un), vertical jump height (cm), Romberg balance test, ball zigzag time (pass 12 cones at 2 m each), zigzag without a ball (pass 12 cones at 2 m each), and shuttle run time (20 m round trip).
Leite et al., (2020) (Brazil)	Athletes (n = 35, M = 15 and F = 20; CRCT)	10 min	DF (n = 20; M/F = 9/11)	DF-sham (n = 15, (M/F = 6/ 9)	Instrumental DF, performed by the therapist. Outcome variables: sEMG (%), isometric strength (kgf); neuromuscular efficiency (kgf/ μs).
Rey et al., (2019) (Spain)	Elite Soccer athletes (n = 18, M; RCT)	20 min	FR (n = 9)	CG (n = 9)	FRSMR on quadriceps, hamstrings, adductors, glutes, and gastrocnemius. Outcome variables: vertical jump height (cm), 5 and 10 m sprint time, Agility T-Test agility time, flexibility (sit and reach), perceived total quality recovery, and VAS scores.

(continued on next page)

Table 1 (*continued*)

First Author/ Year/ Country	Sample/ Genre/ Type of study	Time (Min/ number of sessions)	EG	CG	Intervention and outcome variables
Rhyu et al. (2018) (Korea)	Basketball athletes (n = 40, M; RCT)	40 min (warm-up 10 min) Intervention (30 min) 6x/ week, 8 weeks	ASTM (n = 20)	CG (n = 20)	IASTM performed by the therapist and the Graston technique. Outcome variables: ankle ROM_{active} (with knee flexion at 0 and 45°), side step test (arbitrary units), SJ height (cm), isokinetic ankle strength at 30 and 120°/s, isokinetic knee strength at 60 and 180°/s; Hamstrings/ Quadriceps ratio (cranes/ s), flexibility in cm (sit and reach).
Sağiroğlu et al., (2017) (Turkey)	Athletes (Judo, Karate, Tae Kwon Do, Muay Thai) (n = 16, M; CRCT)	8 min total (2 × 30 s for each muscle)	FR (n = 16)	SS (n = 16)	FR or SS intervention on the hamstrings, quadriceps femoris, glutes, and gastrocnemius. Outcome variables: CMJ height and flexibility (sit and reach).
Wang et al., (2022) (China)	Tennis athletes (n = 27, M; RCT)	7 min total	VFR (n = 9)	PVPD (n = 9); CG (n = 9)	VFR group: VFR at 60 Hz on lumbar, glutes, quadriceps, and lateral thigh muscles. PVPD group: PVPD use; CG: no intervention. Outcome variables: vertical CMJ height, drop test jump (reactive force index), 2.5-m lateral acceleration test, hexagon test, and Y-balance test (%).

Abbreviations: **SS: static stretching; DS: dynamic stretching; CG: control group; EG: experimental group; F: female; M: male; PVPD: portable vibrational percussion device; CRCT: crossed randomized clinical trial; RCT: randomized clinical trial; NRCT: non-randomized clinical trial; CMJ: countermovement jump; SJ: squat jump; FR: foam roller; VFR: vibrational foam roller.ROM_{active}: active range of motion; sEMG: muscle excitation electromyography; IASTM: instrument-assisted soft tissue mobilization; DF: diacutaneous fibrolysis; VAS: visual analog scale (muscle pain perception); VO_{2max}: maximum oxygen volume**.

After rechecking the criteria, the selected studies were reorganized into two topics: 1) sports performance IASTM outcomes related to flexibility, muscle strength, ROM, joint velocity, and sensitivity; 2) FRSMR use and sensitivity-related factors as myofascial release strategies to improve viscoelastic properties, muscle strength, and performance in athletes.

2.6. Risk of bias assessment in the selected studies

The analysis of experimental studies followed the "Cochrane Handbook for systematic reviews of interventions" guidelines (Version 5.1.0) (Higgins and Green, 2011). The Cochrane Handbook (Table 2) was adapted to assess bias considering a study satisfactory and of possible allocation when it reached ≥4 domains from Table 2 (handbook-5-1. cochrane), with a low level of bias. The selected study should have a low risk of bias in four or more domains, as long as the sixth and seventh domains were considered. The study was considered unsatisfactory when it achieved a "low risk of bias" in one, two, or three domains ≤3 domains.

3. Results

3.1. Study selection

A total of 11,346 articles related to the topic of interest were identified in the selected databases. After exclusion of 3491 duplicate articles, 7855 articles in Portuguese, English, and Spanish were selected for analysis. A comprehensive analysis of titles and abstracts eliminated 7699 manuscripts, resulting in 156 included articles. Subsequently, articles were excluded based on the PICO question (n = 129). In the second stage, the 27 remaining articles were reviewed, and 16 were excluded from the analysis, eight for presenting few details in the methods section, five in which the IASTM and FRSMR results were not well elucidated, and three with outcomes not compatible with the objective of this review. Ten studies were included for qualitative synthesis. Fig. 1 shows the flowchart detailing the identification, inclusion, and exclusion process.

3.1.1. General characteristics regarding the type of study and country where it was conducted

Eleven studies were included for qualitative analysis, seven (63.63%) randomized clinical trials and four (36.36%) crossover randomized clinical trials. These studies were conducted in Korea (two, 18.18%), Brazil (two, 18.18%), China (two, 18.18%), Turkey (two, 18.18%), Spain (one, 9.09%), the United Kingdom (one, 9.09%), and Iran (one, 9.09%; Table 1).

3.1.2. The absolute sum of data regarding the number of surveys and scores achieved

As for the scale scores using the Cochrane Handbook tool, five experimental studies had a low risk of bias in five domains, which was the most significant proportion of the low risk of bias, and six scientific studies achieved a low risk of bias in four domains (Table 2).

4. Discussion

4.1. Sports performance IASTM outcomes related to flexibility, muscle strength and power, ROM, joint velocity, and sensitivity

The IASTM strategy changed the tissue's viscoelastic properties, reducing stiffness without reducing performance, as in static stretching (SS) (Leite et al., 2020). The dynamics involve the presence of type 1 endocannabinoid receptors and hyaluronic acid (HA)-rich cytoplasmic vesicles, whose contents are excreted into the extracellular matrix (ECM) (Fede et al., 2020; Forteza et al., 2021; Stecco and Day, 2010). ECM HA is a key element that hydrates and improves tissue turgor and

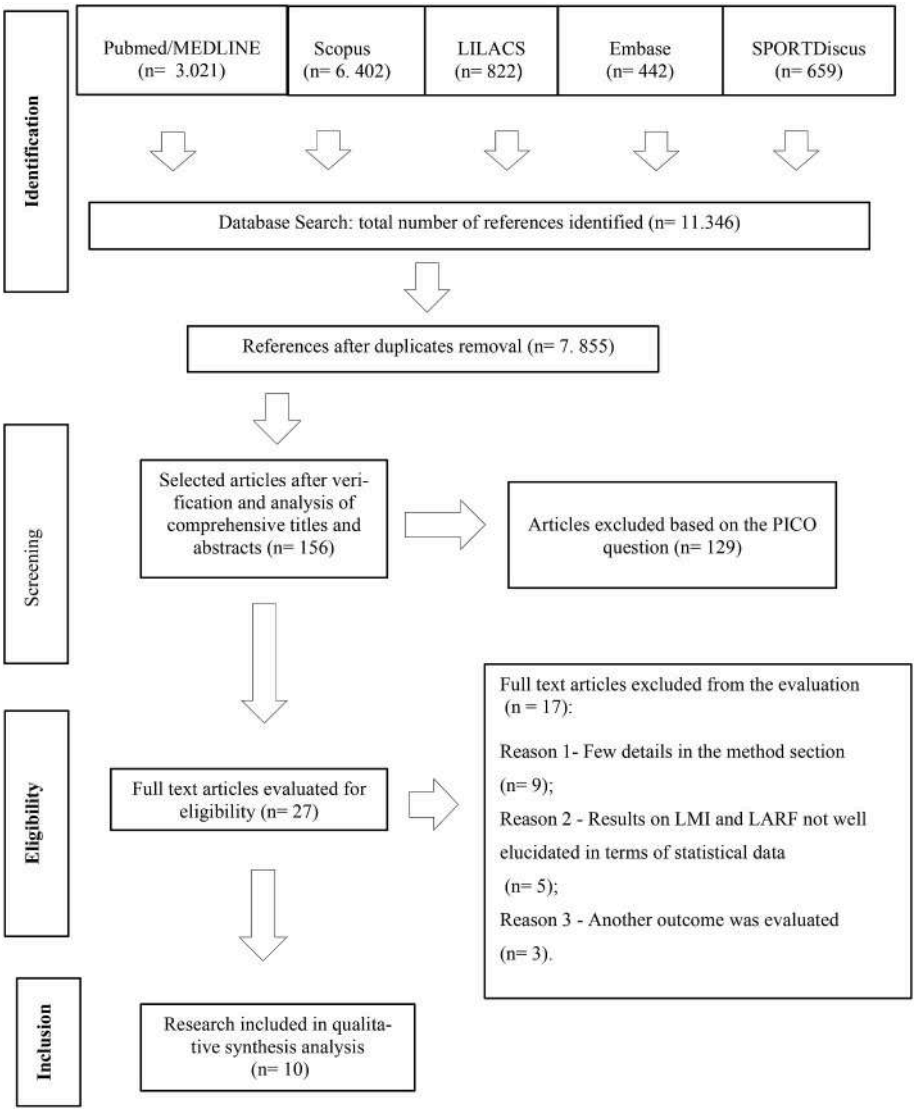

Fig. 1. Prisma flow chart.

Table 2
Experimental studies according to the Cochrane Handbook scale adaptation.

No.	First author	Cochrane Handbook SO/MS	Relative Frequency (%)
01	Blades et al.	4/7	57.1
02	Camargo et al.	4/7	57.1
03	Giovanelli et al.	5/7	71.4
04	Hamzeh Shalamzari et al.	4/7	57.1
05	HSU et al.	5/7	71.4
06	Kim and Yim	5/7	71.4
07	Leite et al.	4/7	57.1
08	Rhyu, Han, and Rhi	5/7	71.4
09	Sağiroğlu et al.	4/7	57.1
10	Wang et al.	5/7	71.4

Abbreviations: SO: score obtained; MS: maximal score.

flexibility. This HA-rich ECM conformation allows for shear strain between layers and tissue adaptability (Fede et al., 2020).

Myofascial release strategies have improved sports performance by using metal equipment to release skeletal muscles (Kim and Yim, 2018; Leite et al., 2020; Rhyu et al., 2018). Diacutaneous fibrolysis (DF) showed greater muscle excitation on electromyography (sEMG; %), with greater effect ($F = 6.93$; $\eta 2 = 0.17$) and greater force with greater effect (Kgf; $F = 7.92$; $\eta 2 = 0.19$). However, there was no difference in post-intervention neuromuscular efficiency compared with the DF-sham group (Leite et al., 2020).

Gastrocnemius stiffness reduces ROM during dorsiflexion, which limits knee flexion during squats and similar tasks. In basketball, the use of IASTM in the active ROM (ROM_{active}) showed greater isokinetic strength in the ankle. In dorsiflexion, the interaction group *vs.* significant time was favorable on both ankles. With the knee at 0° flexion, it pointed $F = 20.313$ ($p < 0.001$), $F = 16.787$ ($p < 0.001$), and at 45°, $F = 24,617$ ($p < 0.001$) and $F = 46,122$ ($p < 0.001$), for the right and lef ankle, respectively. In plantar flexion with the knee at 0° flexion, it showed $F = 17.061$ and $F = 7.625$ (both with $p < 0.001$) and at 45°, $F = 8.217$ ($p = 0.009$) and $F = 24.318$ ($p < 0.001$), for the right and left ankle, respective (Rhyu et al., 2018). In peak torque (PT) by body percentage, the values were equivalent both on the right and left sides, with 30°/s angular velocity for dorsiflexion (right: $F = 14.504$, $p = 0.001$; left: $F = 21.107$, $p < 0.001$) and plantarflexion (right: $F = 58.029$, $p < 0.001$; left: $F = 12.082$, $p = 0.002$) and angular velocity of 120°/s (right: $F = 3.968$, $p = 0.049$; left: $F = 5.938$, $p = 0.023$) and ($F = 31.694$, $p < 0.001$; left: $F = 19.713$, $p < 0.001$), respectively (Rhyu et al., 2018).

Isokinetic ankle strength and power increased when measured at 30°/s and 120°/s angular velocities for plantar flexion and dorsiflexion,

and knee strength increased at 60°/s and 180°/s for flexion and extension (Rhyu et al., 2018). Other authors using IASTM reported relevant results between groups at an angular velocity of 60°/s. The IASTM group showed higher PT in both knee extension and flexion on both right and left sides and indicated an increased PT in flexion in both knees ($p < 0.01$). The quadriceps to hamstring ratio at 60°/s increased significantly only on the right side ($F = 6.725$), with no changes on the left side ($F = 1.654$) (Kim and Yim, 2018).

Improved side step performance is analyzed as a physical fitness component, and soccer-specific technical aptitude is analyzed by decreased execution of zig-zag and zig-zag with ball tests (Kim and Yim, 2018) and balance and shuttle run. The IASTM group presented a higher step count in the postintervention side step test compared to the pre-intervention group and the control group (CG) ($F = 15.263$). The findings showed significant differences in the side step ($F = 15.263$), sit and reach ($F = 5.749$), and squat jumping (SJ) ($F = 15.229$) tests between the IASTM and CG groups, favoring the improvement of these variables in the IASTM group (Kim and Yim, 2018).

The 30°/s angular velocity for plantar flexion showed increased PT proportionally to body weight in both feet, with group interaction *vs.* significant time on the right and left ($F = 16.040$ and $F = 21.598$, respectively) after IASTM. At this same velocity, there was an increase in dorsiflexion ($F = 4.810$ and $F = 46.804$, respectively). At an angular velocity of 120°/s, PT by the percentage of body weight also increased on both the right and left sides for plantarflexion ($F = 32.056$ and $F = 54.979$, respectively) (Kim and Yim, 2018).

As for isokinetic knee strength, there were significant differences between control and intervention groups at 60°/s angular velocity. The IASTM strategy presented higher PT for right and left side extension ($F = 29.818$) (Kim and Yim, 2018). Thus, the findings revealed improved dorsiflexion and plantar flexion at different knee flexion angles. The results favored the different groups that used IASTM compared to the CG, with significantly improved flexibility and PT in different sports (Kim and Yim, 2018; Leite et al., 2020; Rhyu et al., 2018).

4.2. Use of FRSMR and sensitivity-related factors as myofascial release strategies in athletes to improve viscoelastic properties, muscle strength, and performance

The stable FRSMR movement can increase intramuscular tissue temperatures and blood flow, contributing to muscles' viscoelastic properties; the fascia becomes more fluid when affected by heat or pressure (Knight et al., 2001). Otherwise, it densifies, and its viscosity in the solid state increases (Knight et al., 2001). However, the statistical results were not promising regarding sports performance after FRSMR. The intraclass correlation coefficients (ICC) for the 5 and 10 m sprint tests reduced 0.96 (95% confidence interval [95%CI]: 0.92–0.97) and 0.94 (95%CI: 0.90–0.96), respectively. The ICC for the T-test was 0.91 (95%CI: 0.87–0.93), respectively. In the 5 and 10 m sprint tests, FRSMR did not significantly interfere with sprint performance regarding time or time interaction ($p = 0.109$ and $p = 0.200$, respectively) (Rey et al., 2019). This seems to confirm that the SMR should be more targeted to reduce muscle spindle sensitivity and its adaptation rate, thus minimizing the effects of primary and secondary afferents on muscle spindles. Previous studies have reported that FRSMR stresses the tendons during release leading to autogenic inhibition (Schleip, 2003).

Compared with the passive recovery group, the FRSMR group showed a great advantage ($p = 0.038$; effect sizes (ES) = 1.06) in minimizing T-test performance decreases 24h post-training (Rey et al., 2019). However, FRSMR reduced vertical CMJ to 0.95 (95%CI: 0.94–0.97), and CMJ performance decreased in both the FRSMR and control groups 24h after the training session ($p = 0.036$), without significant main effect ($p = 0.461$) (Rey et al., 2019). The sit and reach test showed no significant time-group main effect ($p = 0.162$) or significant time-group interaction ($p = 0.070$) (Rey et al., 2019).

The flexibility test showed no favorable values, with ICCs of 0.99 (95%CI: 0.97–0.99) for time ($p = = 0.162$) and group ($p = 0.424$) or time x group interactiond ($p = 0.070$). The total quality recovery (TQR) and visual analog scales (VAS) showed significant two-way time-group interaction. The FRSMR group had a large effect on TQR ($p = 0.018$, ES = 1.08) and VAS ($p = 0.045$, ES = 10.2) scores compared to the passive recovery group 24h post-training (Rey et al., 2019).

As for energy expenditure during running, the outcomes with FRSMR indicated an tendency for increase compared to pre-training ($p = 0.052$, $+6.2 \pm 8.3\%$), and the maximum power exerted during the muscular power of the lower limbs in the immediate post-intervention period and 3 h after was significantly higher than that observed before and after training, with ($p = 0.002$, $+7.9 \pm 6.3\%$) and ($p = 0004$, $+10.0 \pm 8.7\%$), respectively (Giovanelli et al., 2018). The rate of force development during SJ did not differ between immediate pre- and post-FRSMR or 3 h after in both conditions ($p > 0.05$). The same happened with peak force during SV different between the control and experimental conditions ($p = 0.469$, 0.829, and 0.907 at pre, post, and 3 h post-intervention, respectively). In contrast, the rate of force development assessed during CMJ increased immediately after treatment, reaching significant differences between 3 h pre and post at 200 ms at the beginning of execution force output ($p = 0.024$, +38.9%). These changes coincided with significantly increased peak forces pre, post, and between pre and post (Giovanelli et al., 2018).

Muscle performance seems to strongly impact intervention time, and a contraposition prevails in the results. The effects of FRSMR on the 3-min maximal test conditions indicated a mean power ($p = 0.884$, ES = 0.07; 95%CI mean and difference = -3.3, −26.4–19.7 W) and maximum power ($p = 0.577$, ES = 0.27; 95%CI mean and difference = 39.5–20.3–99.4 W). There was no significant effect of the 3-min maximal test conditions for the Borg CR-10 perceived exertion scale ($p = 0.852$, ES = 0.09; 95%CI mean and difference = -0.11, −0.82–0.60 arbitrary units) and feeling scale ($p = 0.539$, ES = 0.30; mean and difference 95%CI = 1.00, −1.57–3.57 arbitrary units) (Camargo et al., 2021).

Repeated measurements revealed a significantly increased ROM_{active} in the FRSMR group after an eight-week program (Hamzeh Shalamzari et al., 2022). The comparison between residual effects of aerobic running (AR) added to SMR (AR + SMR) or associated with SS (AR + SS) showed no benefits of SMR concerning SS. In contrast, AR + SMR showed a greater flexibility increase than AR + SS only in the first 45 s after the intervention. SS decreased CMJ height over 15 min compared to the preintervention condition and was lower compared to AR + SMR after 10 min (Sağiroğlu et al., 2017).

SMR seems to have no additional effect on athletic performance or flexibility compared to AR, even at different times (30 or 60 s). Therefore, FRSMR showed a more favorable prognosis for CMJ height, drop jump test performance assessed via reactive force index, and the hexagon test (Blades et al., 2022; Sağiroğlu et al., 2017; Wang et al., 2022).

Our review had limitations due to the definition of "athlete". Among the included studies, four did not specify the length of experience (Table 3). This information can influence a comparison analysis between these athletes, who in turn are from different sports. Camargo et al. (2021) and Sağiroğlu et al. (2017) reported sport specific volume training and time of sport experience as inclusion criteria, while Blades et al. (2022) stabilished a weekly aerobic training not-sport specific. Other studies' inclusion criteria to define their sample as athletes were too vague to permit replication (Table 3). We recommend that new studies be carried out and specify more clearly the inclusion and exclusion criteria, age, experience in the sport, as well as volume and level of training, so that the effects of interventions on performance can be reviewed. Definition of athlete should be discussed and more well stabilished in further researches.

5. Conclusion

IASTM can be used in sports preparation to improve muscle response

Table 3
Age, Sport training experience, training volume/level of activity and inclusion and exclusion criteria.

First Author/ Year/Country	Sport	Age (years)	Sport experience	Training volume/ level of physical activity	Inclusion criteria	Exclusion Criteria
Blades et al. (2022) (UK)	Boxing	22 ± 2	≥6 months	Not reported	150 min moderate or 75 min vigorous weekly aerobic activity	Not reported
Camargo et al. (2021) (Brazil)	Cycling	26 ± 5	5.6 ± 5.3 years	4.1 ± 1.3 cycling sessions per week and 1.4 ± 1.4 strength sessions per week	≥6 months of training and an average traveled distance of 150 km/week or the last three months prior to the study	Performing SMFR or any manual therapy technique at last 3 months; any musculoskeletal injury within the past 6 months
Giovanelli et al. (2018) (Turkey)	Soccer, track and field, mountain running, parkour athletes	26.3 ± 5.3	Not reported	9.9 ± 3.5 h/wk	Active sport students	Not reported
Hsu et al. (2021) (China)	Elite table tennis	11.2 ± 2.6 M = 20.7 ± 0.9 F = 20.5 ± 0.9	Overall = 11.2 ± 2.6 years M = 11.2 ± 2.6y F = 11.2 ± 2.6y	Overall = 14.5 ± 8.2 h/wk M = 12.8 ± 8.3 h/wk F = 17.1 ± 7.6 h/wk	Elite table tennins status	(1) Non-Elite table tennins status (2) any musculo skeletal injury in the past 3 months, (3) any neuromuscular; diseases, and (4) taking medicine or supplements that might affect performance
Kim and Yim (2018) (Korea)	Soccer	EG = 16.4 ± 0.8 CG = 16.2 ± 0.7	Not reported	Not reported	Young soccer player healthy men aged 15–17 years with no medical illnesses	No reported
Leite et al. (2020) (Brazil)	Athletes (not specified)	EG = 24 ± 4 CG = 25 ± 5	Not reported	Active: (CG = 6.7%; EG = 10%) Irregular A (CG = 20%; EG = 30%) Irregular B: (CG = 73.3%; EG = 60%)	Not reported	Knee valgus, leg length discrepancy, self reported pregnancy, diagnosis of ankylosing spondylitis, uncontrolled hypertension, transient ischemic attacks, congestive heart failure, diagnosed vestibular dysfunction, presence of neurological signs such as paresthesia and compromised tendon reflexes
Rey et al. (2019) (Spain)	Professional Soccer	26.6 ± 3.7	14.8 ± 2.6 years	5-6 weekly soccer sessions with the team and on average exercised 10 ± 1.7 h/wk	Professional soccer players who participated in full training	Injuries resulting in loss of one or more soccer matches/training sessions in the preceding three months prior to the start of data collection. None of the participants had previous experience of FR exercises.
Rhyu et al. (2018) (Korea)	Basketball team	EG = 17.12 ± 1.82 CG = 17.37 ± 1.62	Not reported	Not reported	High school basketball players living in Seoul	Not reported
Sağiroğlu et al. (2017) (Turkey)	Judo, Karate, Tae Kwon Do, Muay Thai	23.9 ± 3.6	≥5 years	5 training sessions per week (h/wk not reported)	College-aged male athletes with hamstring shortness were selected; minimum of 5 years of continuous sports activity and regular team practices (5 training sessions per week)	No history of problems such as arthritis and ligament injuries and meniscal damage
Wang et al. (2022) (China)	Tennis	20.4 ± 1.3	10 ± 0.7 years	No reported	Male tennis team players	Cardiovascular diseases, musculoskeletal or traumatic injuries and other diseases that could limit normal physical activity

Abbreviations: H/w: hour per week; y: year(s); CG: Control Group; EG: experimental Group.

and neuromuscular efficiency during explosive force production. IASTM showed increased performance and muscle excitability, depending on specific strategies and tools to reach deeper muscle layers. The IASTM strategy changed the tissue's viscoelastic properties, reducing stiffness without reducing performance, as in static stretching and the results favored the different groups that used IASTM compared to the CG, with significantly improved flexibility and PT in different sports. FRSMR was favorable for CMJ between 3 h pre- and post-intervention at 200 ms at the beginning of execution force output, being promising in the interaction between condition versus time for the pressure pain threshold. FRSMR can induce neural adaptations, and direct pressure tends to break fibrous adhesion and restore tissue elasticity, resulting in greater flexibility but not favoring aerobic activity. The time taken for FRSMR application seems to be fundamental for its positive effects, and the present study suggests it should be applied for a period of at least 90 s per muscle group, although further studies are needed since these techniques' duration of effect is not well defined in the literature. However, these findings should be taken with caution as the quality of the studies are low, and high quality research is needed to provide comparations between studies.

Ethical approval

Not applicable.

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CRediT authorship contribution statement

Maria Elisa Duarte França: Investigation, Writing – original draft, Formal Analysis. **Mayane dos Santos Amorim:** Investigation, Writing – original draft, Formal Analysis. **Larissa Sinhorim:** Writing – review & editing. **Gilmar Moraes Santos:** Writing – review & editing, Funding acquisition. **Iramar Baptistella do Nascimento:** Formal Analysis, Methodology, Writing – review & editing.

Declaration of competing interest

The authors have no conflicts of interest to declare. All co-authors have seen and agree with the contents of the manuscript and there is no financial interest to report. We certify that the submission is original work and is not under review at any other publication.

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PLOS ONE

RESEARCH ARTICLE

Peripheral muscle oxygenation, pain, and disability indices in individuals with and without nonspecific neck pain, before and after myofascial reorganization®: A double-blind randomized controlled trial

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Abstract

To investigate whether myofascial reorganization® in the trapezius muscle (MRT) improves peripheral muscle oxygenation and pain tolerance and decreases neck disability index (NDI) scores in individuals with and without nonspecific neck pain (NP) using a double-blind randomized controlled trial. Seventy-five subjects were equally and randomly assigned to three groups: the intervention groups (experimental [EG] and sham sSG]) and the control group (CG). Several inclusion criteria were applied to the intervention groups: male or female, aged 18–32 years, self-reported NP in the last 3 months without a defined cause; at least "soft" pain in session 1 of the NDI, and at least a score of 1 on the Visual Analogue Scale (VAS). The CG was required to have NDI and VAS scores of 0 at recruitment. Intervention: The EG underwent MRT for 10 min, once a week for 6 weeks. Patients with NP in the SG underwent classical massage for the same duration and frequency. Patients in the CG had no pain and underwent no intervention. Data collection was performed using the NDI Questionnaire, a pressure algometer for pain evaluation, and near-infrared spectroscopy for muscle oxygenation measurements. It was registered as NCT03882515 at ClinicalTrials.gov. The NDI score in both the EG ($p<0.001$) and SG ($p<0.001$) decreased after 6 weeks of intervention compared to the CG. The CG demonstrated a lower basal tissue saturation (TSI) index than the EG ($p<0.001$) and SG ($p = 0.02$). The EG demonstrated higher oxyhemoglobin values than the SG ($p<0.001$) and CG ($p = 0.03$). The CG had higher pain tolerance than the EG ($p = 0.01$) and SG ($p<0.001$) post-intervention. MRT increased trapezius muscle oxygenation after 6 weeks of intervention.

Competing interests: The authors have declared that no competing interests exist.

Introduction

Nonspecific neck pain (NP) is a common disorder with a high prevalence in occupational sectors [1, 2]. It is defined as pain in the posterior and lateral aspect of the neck between the superior nuchal line and the spinous process of the first thoracic vertebra that does not present with neurological signs or specific pathologies, such as traumatic sprain or fracture, tumor, and infectious or inflammatory cervical spondylolysis, and has no or minor interference with daily living activities [3–8]. In most cases, a specific diagnosis cannot be made and NP is labeled as non-specific due to its multifactorial etiology [9–11]. The Global Burden of Disease Study stated that NP is the fourth largest physical complaint globally with regard to years lived with a disability [12]. The estimated 1-year incidence of NP has been reported to vary from 10.4–21.3% [13, 14]. NP may occur due to incorrect execution of shoulder or upper limb movements that depend on scapular stabilization during daily activity [15]. Among other factors, scapular stabilization requires control and activation of the rotator cuff and the lower and middle trapezius muscle (TM) fibers [16, 17]. The TM fibers are covered by a connective tissue called the fascia. The fascial system [18] has sufficient blood supply to perform its own functions and contains elastin and collagen fibers that provide plastic and elastic properties. However, the energy demands of the fascia during some activities may generate muscle overload, which may reduce local blood supply [19]. This decrease in tissue blood supply might lead to changes that limit or prevent myofascial tissues from sliding across each other, thereby generating myofascial adherence [20–24]. Several treatment options exist for fascial system dysfunction, including the physiotherapeutic technique of myofascial reorganization® (MR). MR works through mechanotransduction, biotensegrity, and a combination of manual pressure with specific mechanical loads in the myofascial tissue [20, 25] MR involves the recognition of areas and paths of resistance and tension [20] to determine the duration, depth, and direction of the exerted pressure to tissue resistance [26–28]. MR can influence the mechanoreceptors inside the fascia, thus contributing to local fluid dynamics, reducing excessive muscle tension and capillary constriction, and increasing local blood flow [24]. These mechanoreceptors were discovered by Yahia et al. (1992) [29] and Stecco et al. (2013) [30] through histological examination of the fascial tissue. In addition, both author groups affirmed the likely participation of the fascial system in proprioception. A study on the acute effect of MR in individuals with NP was published in 2022 with promising results. The authors observed an increase in the tissue level of oxyhemoglobin [31]. As it only utilizes manual contact, MRT is a simple, non-invasive, non-pharmacological, and low-cost method that could be easily applied in clinical practice. Therefore, we aimed to investigate whether MRT improves peripheral muscle oxygenation as a primary objective and pain tolerance and neck disability index (NDI) scores in individuals with NP as secondary objective.

Materials and methods

Study design

We conducted a double-blind randomized controlled clinical trial. The participants were divided into three groups: (i) the experimental group (EG) who underwent MRT; (ii) the sham group (SG) who underwent classical massage (CM); and (iii) the control group (CG) who received no intervention. The EG and SG included participants with NP. The CG included participants without NP.

Randomization

The participants were initially evaluated by a blinded trained investigator who, using the random number generator application, randomly assigned blocks for the EG and SG in parallel

(1:1), using blinded allocation and intention-to-treat (ITT) analysis. During randomization, the participants with NP either underwent MRT or CM. The therapist did not participate in the selection and was blinded during the allocation. However, we could not blind the therapist regarding the groups. CM is a continuous superficial sliding technique, associated with benefits and wellbeing [32]. A CG of individuals without NP underwent an evaluation before and after 10 min, without any intervention.

Population and sample

The study was approved by the Ethics and Research Committee on Human Beings of the Santa Catarina State University (protocol number: 2.630.855) on May 02, 2018. The study was registered as NCT03882515 at ClinicalTrials.gov on March 27, 2019. We confirm that all ongoing and related studies for this drug/intervention are registered. Each participant provided Informed written consent. Several inclusion criteria were applied to the intervention groups: participants of both sexes, aged > 18 years, with self-reported NP in the last 3 months without a defined cause. The NP should have specifically occurred in the TM during daily activities or work. Additionally, they should have had at least "soft" pain in session 1 of the NDI and at least a score of 1 on the Visual Analogue Scale (VAS). The CG was required to have scores of 0 for the NDI and VAS at recruitment. The CG were matched with the EG according to age, sex, and BMI, due to the relevance of these variables to the fascia. Several exclusion criteria were applied for both groups: neurological disease, history of trauma or surgery on the cervical spine, clinical diagnosis of disc herniation or nerve compressions, and previous physical therapy (3 months). Individuals who met the inclusion criteria and provided informed consent were invited to participate in the study. We informed participants about the possibility to withdraw their participation at any phase without penalty or constraints. We preserved the personal identification of all participants, due to the possibility of scientific dissemination of the results. Data were collected at the Santa Catarina State University. The participants were recruited using convenience sampling and allocated to the aforementioned groups. Data collection was carried out from August 2018 to July 2019.

Sample calculation

We estimated the number of participants for each group using the G*Power 3.0.10 software, with analysis of variance with repeated measures for intra-and inter-participants considering the three independent groups (EG, SG, and CG). A total sample of 54 participants (18 per group) provided a power of 95% and an effect size of 0.25 (Cohen's d), once that there was no study to be based as expressed in Table 1. The type I error was fixed at the conventional level (5%). We defined the number of participants in each group using the key characteristics of the study, such as the study design, primary outcome, and variability–Fig 1 details the flow of patients.

Instrumentation

We used a near-infrared spectroscopy (NIRS; Artinis®, Portamon system, Netherlands), pressure algometer (JTech Commander Algometer®, USA), NDI questionnaire, [33] and VAS [34].

Anthropometric measurements. We measured the participants' stature using a stadiometer (Standard Sanny—American Medical do Brasil Ltda, São Paulo, BRA) and body mass using a digital scale (Mettler-Toledo, Inc., Columbus, Ohio, USA®). Each participant's BMI was calculated using these variables.

Table 1. d-value in comparisons between groups.

Outcome Measure	Group/Time	Mean (Pre)	SD (Pre)	Mean (Pos)	SD (Pos)	Cohen's d
ΔO2Hb (μMol/l)	Experimental	0.81	1.51	0.62	2.66	-0.621
ΔHHb (μMol/l)		0.07	0.77	-2.1	8.31	-0.103
ΔtHb (μMol/l)		0.71	2.48	0.69	1.89	0.187
TSI (%)		77.8	4.99	80.93	4.59	0.614
ΔO2Hb (μMol/l)	Sham	-0.16	1.45	-0.62	1.85	-0.778
ΔHHb (μMol/l)		0.62	1.06	-0.11	1.86	0.225
ΔtHb (μMol/l)		1.36	3.95	-0.47	2.87	-0.561
TSI (%)		77.72	5.79	78.5	3.75	0.219
ΔO2Hb (μMol/l)	Control	-0.19	1.33	0.45	1.27	-0.621
ΔHHb (μMol/l)		1.67	6.03	-0.05	0.65	-0.103
ΔtHb (μMol/l)		-0.16	1.97	-0.3	1.53	0.187
TSI (%)		75.36	4.98	75.54	5.16	0.614
Pain	Experimental	51.08	27.65	64.24	25.92	0.079
	Sham	42.78	22.69	45.58	27.91	-0.287
	Control	70.49	32.29	81.24	27.8	0.079
Neck disability index	Experimental	21.12	7.73	13.68	8.76	-1.234
	Sham	18.12	7.46	13.96	8.18	-0.751
	Control	5.48	5.58	5.08	6.98	-1.234

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Near-infrared spectroscopy. We used NIRS (PortaMon®, Artinis, Netherlands) to measure peripheral muscle oxygenation. NIRS primarily depends on the relative transparency of a tissue to light and the light-absorbing characteristics of oxygenated hemoglobin. It continuously displays relative changes in hemoglobin concentration using different wavelengths (light-emitting diodes: 3×2 wavelengths). NIRS is wireless, non-invasive, accessible, and allows continuous measurement to be performed in a laboratory or even outdoors, without the need for special infrastructure [35].

Pressure algometer. We used a digital algometer (JTech Commander Algometer®, USA) for quantitative assessment of pain pressure thresholds (PPT). The pressure algometer provides a semi-objective, reliable, and efficient assessment for treatment planning and evolution monitoring [36].

Neck disability index. The NDI is a 10-item questionnaire designed to assess functional disability and pain around the cervical spine. It has been adapted and validated in the Brazilian Portuguese language [37]. Each item comprises six responses that are connected to a routine activity, except for question five, which is related to headaches. Responses are numbered from 0–5 and are associated with the degree of cervical pain and its interference with routine activities. The scores were calculated and converted into a percentage value and only the items answered were considered [33].

Visual Analog Scale. The VAS is a one-dimensional instrument used to assess subjective pain intensity. It comprises a line numbered from 0–10, wherein 0 corresponds to "no pain," and 10 corresponds to the "the worst imaginable pain" [34].

Outcome parameters

For each set of analyzed repetitions (3×3 matrix; three evaluations in three groups), several parameters were extracted: peripheral muscle oxygenation (oxyhemoglobin, O_2Hb), deoxyhemoglobin (HHb), total hemoglobin (tHB), and the tissue saturation index (TSI) at the time of

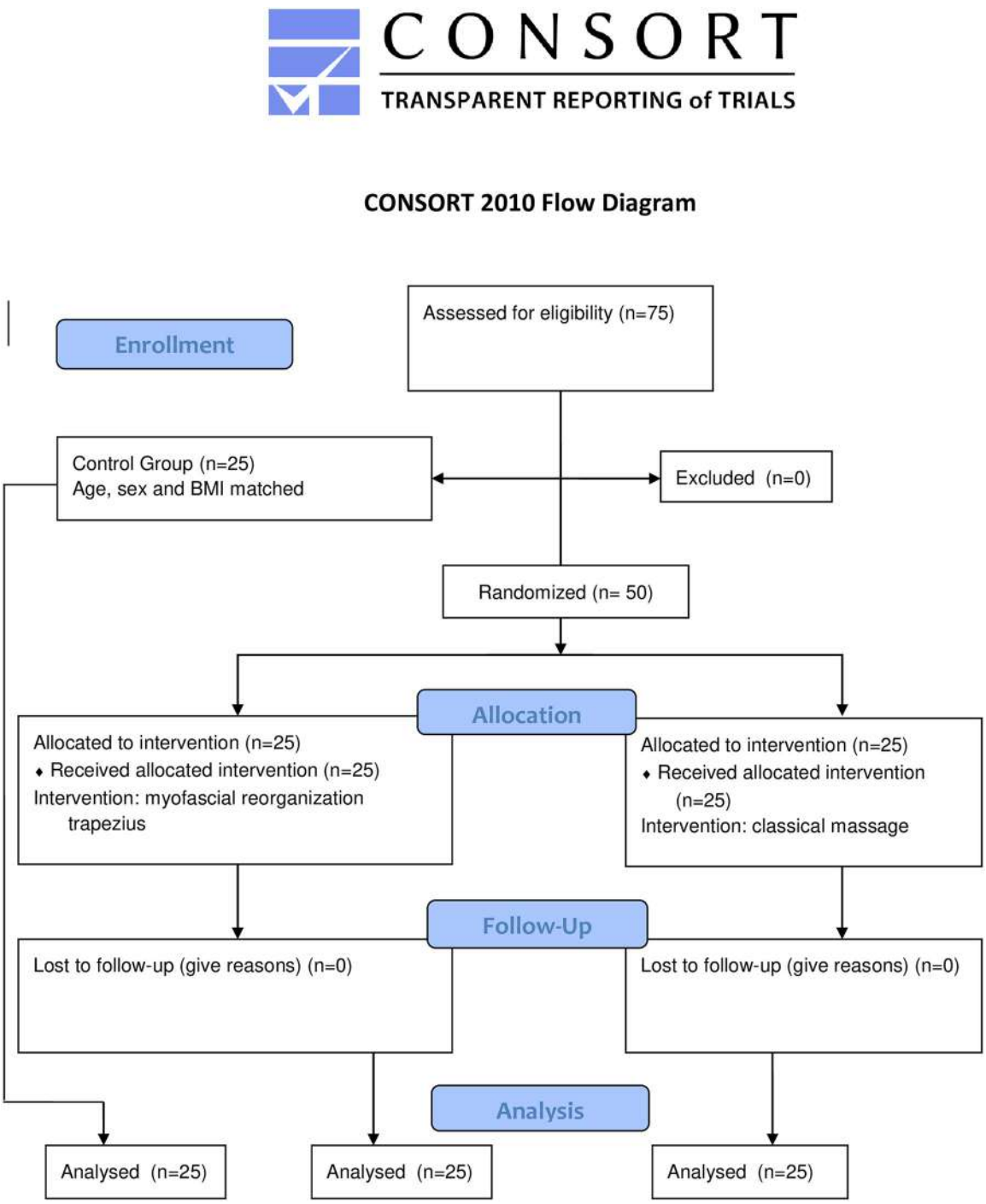

Fig 1. Flow diagram.

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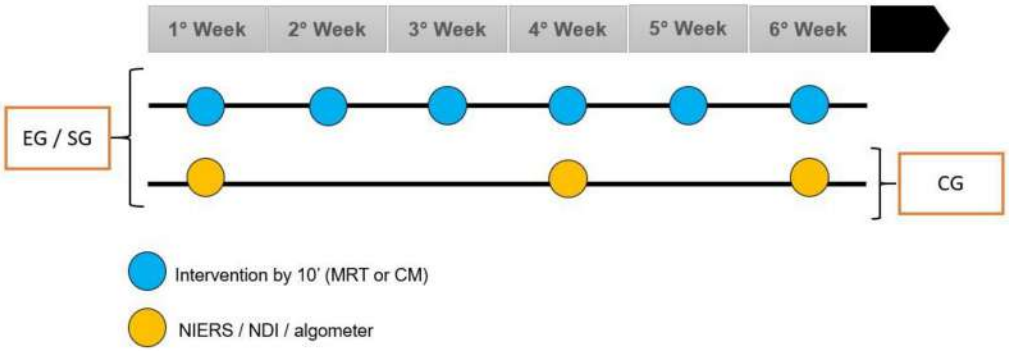

Fig 2. Data collection procedure scheme. Abbreviations: EG, experimental group; SG, sham group; CG, control group; MRT, myofascial reorganization® trapezius muscle; CM, classical massage; NIRS, near-infrared spectroscopy; NDI, neck disability index.

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interest (before and immediately after the intervention). Other parameters, such as subjective pain intensity, pain tolerance, and NDI, were measured before the interventions.

Data collection procedures

Participants were evaluated by a blinded evaluator who collected their personal (name, address, telephone, and age) and anthropometric data (stature and body mass). Thereafter, NDI and VAS scores were evaluated, followed by NIRS and algometer measurements in a separate intervention room. The rooms were maintained at a controlled temperature (24˚C) during the measurements and interventions.

Primary outcomes. Muscle oxygenation was measured before and after the intervention, or after 10 min rest for the CG. Skin was cleaned with alcohol, following which the device was positioned bilaterally in the middle fibers of the TM, based on the Surface ElectroMyoGraphy for the Non-Invasive Assessment of Muscles (SENIAM) recommendations) in contact with the skin. Those with hairy skin underwent trichotomy using disposable and individual blades. The equipment was covered with a black cloth to avoid light penetration. The acquisition frequency was 10 Hz. The data collection procedure comprised six steps of intervention/evaluation (Fig 2).

Secondary outcomes. To assess pain tolerance, the participants were seated on a backless chair and an algometer was positioned bilaterally in the middle fibers of the TM at the T3 level, according to SENIAM recommendations [38]. The evaluator applied pressure perpendicular to the skin until the pressure pain tolerance was acknowledged by the participant [39]. The procedure was repeated twice on each side of the TM.

The EG and SG underwent the MRT and CM, respectively, once a week for 10 min, for 6 weeks. The CG underwent three assessments during the 6 week period (weeks 1, 4, and 6). Following evaluation using NIRS, NDI, algometer, and VAS, the participants were requested to rest for 10 min, followed by repeat measurements. In cases of absences, the intervention was postponed for a week as participants had to receive six interventions to conclude the study.

Interventions

The protocols were performed by the same trained physiotherapist and each session lasted 10 min. The MRT followed the protocol published by Sinhorim et al. (2019) [20] and Amorim et al. (2022) [31]. This manipulation technique emphasizes specific mechanical loads directed

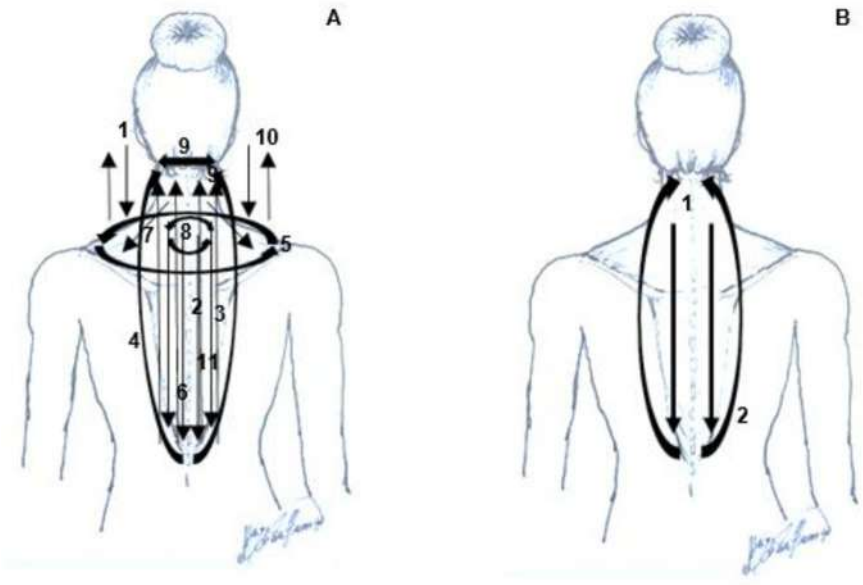

Fig 3. A schematic of the protocols performed: (A) MRT and (B) CM techniques (SINHORIM, et al., 2019). (A) (1): Participants began in a side position. Pressure was applied with a closed fist and movement in shear in the medium fibers of the TM. (2–9): Participants were moved to a prone position. (2–3) Sliding along the TM to the base of the skull, (4) Sliding of the T12 level around the lateral edge of the scapula to the axilla, (5) Sliding forming a canoe from one acronym to another, passing above and below the level of T1, (6) Compression in the caudal direction from the upper to the lower TM in the thenar region, (7) Sliding of the proximal and distal insertion of TM medial fibers, (8) Sliding bypassing the T1 spinous process, and (9) Sliding transversely at the upper insertion of the upper TM fibers. (10) Participants were moved to the supine position and tweezer traction of the TM fibers was performed. (11) Participants were seated with their hands in a fist, and continuous clamping and shear on the TM was performed. (B) (1) Participants were placed in a prone position. Continuous superficial displacement at the lateral edges of the TM followed the directional movement of the lower, medium, and upper fibers. (2) Caudal–cranial return of the technique. Abbreviations: MRT, myofascial reorganization® trapezius; CM, classical massage; TM, trapezius muscle.

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to the fascial tissue. The CM technique was based on the studies by Domenico and Wood (1998) and Kong et al. (2013) [32, 40]. The intervention room had a stretcher, chair, and bathroom for the convenience of the participants. Fig 3 provides a schematic representation of the protocol.

Data processing and statistical analyses

We extracted the muscle tissue oxygenation data (HbO_2, HHb, tHB, and TSI [%] concentrations) using dedicated software (Oxysoft®, Artinis, Netherlands). The deltas of variations in the obtained concentrations were calculated, and the average tissue oxygen saturation was calculated before and immediately after the intervention. The PPT data were obtained from the equipment and extracted from the mean of two bilateral measurements. We calculated the NDI scores for each participant and the VAS was registered before the interventions or after 10 min rest for the CG. The data were initially tabulated in Microsoft Excel using the Windows 10 operating system. Then, they were converted to the Statistical Package for the Social Sciences software (SPSS) version 20.0. To verify the normal distribution of the sample, the Kormogorov-Smirnov test was applied. Descriptive statistics were used to characterize the participants through means and standard deviations. To analyze whether MRT mediated changes in muscle oxygenation (HbO2, HHb, tHB, and TSI), a statistical model was constructed based on inter- and intra-group comparisons using a general linear variance analysis

(repeated measures 3×3). This helped detect differences between the mentioned variables across different periods. The level of significance was set at $p \leq 0.05$. The results were reported in accordance with CONSORT. In all comparisons, a primary ITT analysis including all randomized participants was performed. For ITT analysis, missing data were filled in using simple imputation, being replaced by the last value collected from the participant for the variable in question.

Results

This study included 56 females and 19 males aged 18–39 years, who were divided into three groups, (EG, SG, and CG). A total of 300 interventions were performed during the 6 week intervention period across the EG (MRT) and SG (CM). Table 2 summarizes the sample characteristics.

Table 3 depicts the TM oxygenation values, qualitative and quantitative pain results, and the NDI scores for the groups.

NDI findings

We observed an interaction (weeks × groups) between the NDI results ($F(1, 272) = 7.310$; $p<0.001$). Following 6 weeks of treatment, we observed a significant reduction in the functional disability scores in the EG ($p<0.001$) and SG ($p<0.001$) compared to the CG (Table 3). After six interventions, the EG, SG, and CG demonstrated score decreases of 35.22%, 22.95%, and 8.96%, respectively.

Pain tolerance

There was an increase in PPT ($F(1, 172) = 18.083$; $p<0.001$) from week 1 to week 6 ($p<0.001$) and from week 4 to week 6 ($p<0.001$; Table 3). The differences between groups were statistically significant ($F(1, 172) = 10.553$; $p<0.001$). Regardless of the week of evaluation, the CG demonstrated greater PPT than the EG ($p = 0.01$) and SG ($p<0.001$). At the end of the treatment, the EG, SG, and CG demonstrated 25.8%, 6.5%, and 15.3% increases in PPT respectively. Therefore, the percentage increase in PPT was greater in the EG.

Table 2. Anthropometric characterization by group.

	EG	SG	CG	P value
Gender (male and female)	7 and 18	5 and 20	7 and 18	
Age (years)	22.60±3.85 male (23.71±1.93) female (22.17±0.79)	22.56±3.75 male (24.20±2.49) female (22.15±0.71)	22.64±3.80 male (23.71±1;92) female (22.22±0.76)	0.997
Mass (kg)	67.00±14.78 male (77.62±5.31) female (62.86±3.10)	64.60±10.68 male (73.10±5.10) female (62.48±2.15)	65.20±11.52 male (79.86±2.91) female (59.50±1.55)	0.779
Stature (m)	1.67±0.08 male (1.75±0.02) female (1.64±0.01)	1.64±0.06 male (1.73±0.01) female (1.62±0.01)	1.67±0.08 male (1.78±0.02) female (1.62±0.01)	0.360
BMI (kg/m^2)	23.84±4.78 male (25.56±2.38) female (23.21±0.96)	23.80±3.15 male (24.26±1.25) female (23.68±0.73)	23.14±2.50 male (24.95±0.79) female (22.43±0.55)	0.731

Data are expressed as mean±standard deviation. EG, experimental group; SG, sham group; CG, control group; kg, kilogram; m, meters; BMI, body mass index.

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Table 3. Peripheral muscle oxygenation, pain, and neck disability index scores across the studied groups (EG: 25; SG: 25; and CG: 25) during the 1st, 4th, and 6th weeks of evaluation.

Variables	1st Week			4th Week			6th Week		
	EG	SG	CG	EG	SG	CG	EG	SG	CG
ΔO_2Hb (μMol/l)	0.81±1.51	-0.16±1.45	-0.19±1.33	1.28±2.36	-1.18±1.76	0.82±2.97	0.62±2.66	-0.62±1.85	0.45±1,27‡
ΔHHb (μMol/l)	0.07±0.77	0.62±1.06	1.67±6.03	0.008±1.15	0.49±1.12	0.26±1.04	-2.10±8.31	-0.11±1.86	-0.05±0.65
ΔtHb (μMol/l)	0.71±2.48	1.36±3.95	-0.16±1.97	0.87±3.30	-0.65±2.14	0.61±3.05	0.69±1.89	-0.47±2.87	-0.30±1.53
TSI (%)	77.80±4.99	77.72±5.79	75.36±4.98	79.90±7.29	79.26±5.35	75.62±4.48	80.93±4.59*	78.50±3.75	75.54±5.16
Pain (Kgf)	51.08±27.65	42.78±22.69	70.49±32.29	53.15±22.78	42.07±28.18	78.55±29.93	64.24±25.92	45.58±27.91	81.24±27.80
NDI (%)	21.12±7.73	18.12±7.46	5.48±5.58	17.88±8.81	17.36±7.68	5.76±6.19	13.68±8.76†	13.96±8.18†	5.08±6.98

Data are expressed as mean ± standard deviation; EG: experimental group, SG: sham group, CG: control group, ΔO_2Hb: oxyhemoglobin, ΔHHb: deoxyhemoglobin, ΔtHb: total hemoglobin, TSI: tissue saturation index, μMol / l: micromol per liter, %: percent, Kgf: kilogram force, NDI: Neck Disability Index.

*Statistically significant EG values compared to the 1st week ($p<0.001$) for TSI;

†statistically significant values of EG ($p<0.001$) and SG ($p<0.001$) for NDI (ANOVA test of repeated measures); and

‡ statistically significant EG values when compared to the SG ($p<0.001$) and CG ($p = 0.03$) for O_2Hb.

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Peripheral muscle oxygenation

The TSI findings revealed a significant difference between the groups ($F(1, 272) = 7.206$; $p<0.001$). The CG demonstrated a lower baseline TSI than the EG ($p<0.001$) and SG ($p = 0.02$). The percentage increases in the EG, SG, and CG were 4.02%, 1%, and 0.23%, respectively. The EG presented higher ($F(2, 172) = 11.699$; $p<0.001$) HbO2 values than the SG ($p<0.001$) and CG ($p = 0.03$) and demonstrated a positive percentage variation (post-treatment – pre-treatment) across the treatment duration. This behavior differed from that of the SG and CG, which occasionally demonstrated negative variation. Other variables (ΔHHb and ΔtHb) related to peripheral muscle oxygenation did not demonstrate significant differences between the groups and weeks.

Discussion

Our findings revealed that MRT modified pain tolerance, peripheral muscle oxygenation, and NDI among individuals with and without NP at three time points (before and after the 1st, 4th, and 6th intervention), thereby confirming our hypothesis. This is the first study to use this methodological proposal.

The EG demonstrated an increase in TSI relative to the CG, in addition to a higher percentage increase (4.02%) in tissue saturation than the SG and CG. Moreover, the EG had a higher PPT increase (25.8%) than the SG (6.5%) and CG (15.3%). The EG and SG presented lower functional disability scores, indicating less disability at the end of the treatment. The EG exhibited a a greater reduction in functional disability scores (35.22%) than the SG (22.95%). In a recently published study, 50 participants (female: 36, male: 14) with and without nonspecific NP were assigned to either the EG (25 participants with NP), who underwent MRT or the CG (without NP) who did not undergo the intervention. TM oxygenation was measured using NIRS before and after a single intervention. All participants were tested and re-tested after 10 min. Results indicated that after 10 min of MRT, the level of oxygenoglobin in the middle fibers of the trapezius increased (0.72 ± 1.47 vs. −0.14 ± 1.33 mmol/dL, $p = 0.01$) [40].

These findings corroborate the results of a previous study that comprised 59 individuals with NP who underwent 10 treatment sessions across 4 weeks, each lasting 15 min. The treatment consisted of analgesic superficial thermotherapy and transcutaneous electrical

stimulation (50 min) with either manipulation therapy or MRT in the sternocleidomastoid, supra, and infrahyoid muscles and posterior rectus head muscle [41]. The researchers observed significant pain reduction in both groups. This reduction was greater in the group that received MRT (22.1–16.0) than the group that underwent manipulation therapy (24.5–20.0). However, this difference was not significant. Similarly, we observed a significant difference in PPT between those who underwent MRT and CM at the end of the treatment.

Our study demonstrated increased PPT in the group that received MRT after six interventions. Our findings were similar to that of another study that allocated 41 participants with NP [42] to two groups: those who received MRT (five 45-min sessions) and those who underwent ultrasound therapy, transcutaneous electrical nerve stimulation, and massage (10 sessions across 2 weeks). The authors concluded that MRT was better than a multimodal physiotherapy program for pain improvement.

Several chronic and persistent dysfunctions are supposedly related to transmission of prolonged nociceptive signals to peripheral myofascial tissues, which sensitize the central nervous system and increase its excitability [43]. Pro-inflammatory processes [44] cause nociceptive stimuli [45] and trigger momentaneous adaptations in endogenous pain modulation [46]. At the end of 6 weeks, we observed a greater percentage increase in PPT in the EG (25.8%) than in the SG (6.5%). This could have been caused by the MRT-promotedremodeling through mechanotransduction, which is a force applied to the molecular mechanical system that triggers intracellular biochemical exchanges [41], thus, leading to analgesia.

Muscle pain can occur due to intramuscular hypoperfusion, [47] which involves the impairment of muscle tissue microcirculation, resulting in nociceptive pain. Disturbances in muscle microcirculation can produce increased nociceptive neuronal activity by sensitizing the regional muscle nociceptors. In our study, the symptomatic participants (EG and SG) primarily comprised sedentary university students who spent long hours in a sitting position, overloading the TM and, thus, possibly constantly stimulating nociception. This corresponds to the findings of Cagnie et al. [48], who analyzed workers who stayed at the computer for at least 4 h per day.

Performing TM-related movements can decrease muscle oxygenation, as reported by Elcadi et al., [49] who investigated oxygenation in the TM during a 5 min low-intensity contraction (10%). The authors observed a significant decrease in oxygenation during contraction. Other researchers [50, 51] have investigated the TSI in the middle third of the upper TM using NIRS and observed a decrease in muscle oxygenation during repetitive work, from 83.1% to 77.4%. In our study, following MRT, a higher percentage increase in TSI as seen in the EG (4.02%) than the SG and CG (1% and 0.23%, respectively) after six interventions. Our results corroborate those of Schah et al,. [52] who reported an oxygenation increase in the lumbar paravertebral muscles of asymptomatic individuals 30 min post-MRT implementation.

According to some studies [53–55], individuals with myofascial dysfunction experience intramuscular pressure and mechanical compression of the vessels that supply the TM. These changes can be attributed to the presence of myofascial adhesions [56] that decrease the blood supply to the muscle. This alteration in perfusion generates a consequent inefficiency of aerobic metabolism (decreased oxygenation) [57], which results in use of anaerobic metabolism, which creates a greater propensity for muscle fatigue [58].

MRT facilitates readjustment of myofascial structures, thereby increasing muscle oxygenation immediately following its application. Our results supported this premise, as MRT significantly altered the TSI and HbO_2 and, consequently, peripheral muscle oxygenation.

Study limitations

The present study has several limitations that should be acknowledged when interpreting the findings. Firstly, it is important to acknowledge that the aforementioned limitations arise from the lack of complete control over external variables, such as medication use, frequency of physical activity, and stress levels. These factors, which may have influenced the outcomes, were particularly relevant given that the sample predominantly consisted of undergraduate students. Moreover, the study did not assess the menstrual cycle of female participants or their caffeine intake on the day of the intervention.

Additionally, it is worth noting that the reassessment was conducted immediately after the final intervention, thereby limiting the availability of additional data points for analysis. To gain valuable insights into the long-term effects of the intervention, it is recommended to consider a more extended follow-up period or conduct multiple reassessments at different time points.

Furthermore, while the study revealed a statistically significant difference in NDI (Neck Disability Index) between the groups over multiple weeks, and an acceptable effect size was observed, caution is advised in interpreting these results. The absence of the recommended 8.4-point difference in pain intensity between the groups, as suggested by Jorritsma et al. (2012) [59], indicates a potential limitation in the clinical significance of the observed results.

Lastly, it is important to consider the limited feasibility of establishing the minimum clinically important difference for the Visual Analog Scale (VAS) within the specific context of the Brazilian population. The lack of established guidelines for the VAS in this context introduces uncertainty and hinders the comprehensive interpretation of pain intensity outcomes.

These identified limitations underscore the need for further investigation and consideration when assessing the implications of the study. Future research endeavors should aim to address these limitations by employing larger sample sizes, incorporating culturally specific guidelines for outcome measures, and exploring alternative methodologies to determine clinically significant differences in pain intensity.

Conclusion

This study provides initial evidence that a 6-week regimen of weekly 10-minute myofascial reorganization® (MR) sessions may improve trapezius muscle tissue oxygenation and peripheral blood flow among patients with neck pain. While the experimental group (EG) and sham group (SG) demonstrated statistically significant improvements in trapezius muscle tissue saturation index (TSI) compared to the control group (CG), the between-group differences in self-reported pain and disability scores did not exceed minimal clinically important difference (MCID) thresholds. This indicates that despite measurable physiological changes, the clinical meaningfulness of MR in altering patient-centered outcomes remains unclear in this sample. Future studies should investigate optimal MR parameters (frequency, duration) and include longer follow-up periods to assess sustainability of effects. Combining MR with other evidence-based interventions may also be worthwhile to determine any additive or synergistic benefits for individuals with neck pain.

In conclusion, this preliminary study showed that MR can induce measurable improvements in tissue perfusion in patients with neck pain. However, future randomized controlled trials are needed to confirm the efficacy and generalizability of these findings.

Supporting information

S1 Checklist. CONSORT 2010 checklist of information to include when reporting a randomised trial*.
(DOC)

S1 File.
(XLSX)

Acknowledgments

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Review

Potential Nociceptive Role of the Thoracolumbar Fascia: A Scope Review Involving In Vivo and Ex Vivo Studies

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Abstract: Nociceptive innervation of the thoracolumbar fascia (TLF) has been investigated over the past few decades; however, these studies have not been compiled or collectively appraised. The purpose of this scoping review was to assess current knowledge regarding nociceptive innervation of the TLF to better inform future mechanistic and clinical TLF research targeting lower back pain (LBP) treatment. PubMed, ScienceDirect, Cochrane, and Embase databases were searched in January 2021 using relevant descriptors encompassing fascia and pain. Eligible studies satisfied the following: (a) published in English; (b) preclinical and clinical (in vivo and ex vivo) studies; (c) original data; (d) included quantification of at least one TLF nociceptive component. Two-phase screening procedures were conducted by a pair of independent reviewers, after which data were extracted and summarized from eligible studies. The search resulted in 257 articles of which 10 met the inclusion criteria. Studies showed histological evidence of nociceptive nerve fibers terminating in lower back fascia, suggesting a TLF contribution to LBP. Noxious chemical injection or electrical stimulation into fascia resulted in longer pain duration and higher pain intensities than injections into subcutaneous tissue or muscle. Pre-clinical and clinical research provides histological and functional evidence of nociceptive innervation of TLF. Additional knowledge of fascial neurological components could impact LBP treatment.

Keywords: fascia; in vivo; ex vivo; innervation; pain; thoracolumbar fascia; nociceptor; lower back pain; scoping review

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1. Introduction

The process by which intense thermal, mechanical or chemical stimuli are detected by a subpopulation of nociceptive peripheral nerve endings is called nociception [1–5]. Nociceptors have a peripheral and central axonal branch that innervates their target organ and spinal cord, respectively [1,2,6,7]. Their cell bodies are located in the dorsal root ganglia (DRG) for the trunk and extremities and in the trigeminal ganglion for the face [8–10]. There are two major classes of nociceptors [1–3,6,7]. The first includes medium diameter myelinated (Aδ) afferents that mediate acute, well localized nociception [2–4,6,7]. The second class of nociceptor includes small diameter unmyelinated "C" fibers that convey poorly localized nociception. Most C fibers are polymodal (heat and mechanical sensitive) [2–4,6,7]. Often, heat-responsive unmyelinated afferents develop mechanical sensitivity only in the injury setting [11]. These afferents are more responsive to chemical stimuli (capsaicin or histamine) and are likely to come into play when the chemical milieu of inflammation changes their properties [1,2,12–14]. However, not all C fibers are nociceptors. Some respond to innocuous cooling, while others respond to innocuous stroking of the hairy skin and appear to mediate pleasant touch [15].

C nociceptive fibers project to the superficial dorsal horn (laminae I & II) of the spinal cord, which is organized into anatomically and electrophysiological distinct laminae [1,2,6,7]. The heterogeneity of C fibers has been demonstrated by their neuroanatomical and molecular characterization [16]. For example, the so-called peptidergic population of C nociceptors release the neuropeptides, substance P, and calcitonin gene-related peptide (CGRP); the nonpeptidergic population of C nociceptors express the c-Ret neurotrophin receptor that is targeted by glial-derived neurotrophic factor (GDNF) [1,2,17]. It has been demonstrated that CGRP and SP can act synergistically to promote inflammation and nociceptor sensitization, since they are released by the peripheral or central projections of primary afferent neurons [18,19]. In the periphery, CGRP and SP induce the production and release of inflammatory cytokines, thus contributing to the peripheral sensitization of nociceptive neurons [20]. Centrally, when released into the spinal cord, CGRP and SP also induce central sensitization by acting on dorsal horn neurons [21]. Interestingly, it has been shown that CGRP can inhibit the degradation of SP and thus prolong its action [22]. Finally, CGRP may contribute to mechanical hyperalgesia or allodynia by enhancing the response of wide dynamic range neurons to cutaneous stimulation [23,24].

Musculoskeletal (MSK) pain is defined as acute or chronic pain that affects bones, muscles, ligaments, tendons, and even nerves [25–30]. According to the World Health Organization (WHO), 1.75 billion people have some form of chronic MSK pain [31]. Inadequately managed MSK pain can adversely affect quality of life and impose significant socioeconomic problems. For example, lower back pain (LBP) is the main contributor to disability worldwide [25–30]. However, the mechanisms that underlie its development remain poorly understood [26–30]. It has been demonstrated that there is nociceptive innervation in connective tissues associated with nerves [32], tendons [33], and joints [34–38]. Together, these findings strongly suggest a role in the etiology of pain, and additional studies of nociceptive innervation of connective tissue will help to relate connective tissue dysfunction with LBP [39,40]. To date, it has been demonstrated that when healthy subjects underwent an injection of hypertonic saline into the thoracolumbar fascia (TLF), it resulted in pain of greater intensity, more unpleasant quality, and spreading over a greater area of the back and lower limbs, compared to similar injections into muscle or subcutaneous tissue [41–44]. Furthermore, this pain was associated with chemical stimulation rather than mechanical distention [42]. These studies suggest that the TLF makes a distinct contribution to nociception.

The TLF is a major connective tissue structure that can resist high tensile loads due to its fibers being oriented in multiple planes [45–47]. It has been shown that the thoracolumbar fascia shear strain was ~20% lower in human subjects with chronic lower back pain [48]. TLF consists of several layers. The posterior layer covers the deep muscles (deep lamina) of the back and attaches with the spinous processes via the supraspinous

ligament. This posterior layer of the TLF consists of two separate laminae. The superficial lamina forms a continuation of the aponeurosis of the latissimus dorsi muscle as well as of the aponeurosis of the gluteus maximus muscle. It usually contains many dense collagen fibers crossing to the contralateral side below L2, which constitutes a very rare feature within mammalian anatomy and is probably associated with a contralateral force transmission between latissimus dorsi on one side and the gluteus maximus of the opposite side during human locomotion. This layer is also continuous with the external oblique musculature [49]. Anterior is the deep lamina, which blends with the supraspinous ligament cranially and with the long head of the biceps femoris muscle via the sacrotuberous ligament caudally [50,51]. The deep lamina is usually much thinner than the superficial lamina. Both laminae contain a multitude of smaller blood vessels, but do not contain any large arteries or veins [52,53]. Although the biomechanical properties of TLF are extensively documented and discussed in the literature, the neural properties have relatively received very little attention to date [39].

Despite nociceptive innervation of the TLF having been investigated over the past few decades in various animal models and humans using neuroanatomical and molecular techniques, these studies have not been compiled and their collective findings appraised. The purpose of this scoping review was to assess current scientific knowledge on the nociceptive innervation of the TLF in animal and human in vivo and ex vivo experiments to act as a resource for future clinical research targeting TLF in clinical treatment.

2. Materials and Methods

A scoping review methodology was selected to compile and evaluate data relating to the current state of scientific knowledge available in the literature related to TLF nociception and to identify the gaps that need to be addressed. The framework chosen was based on the guidelines provided by Arksey e O'Malley (2005) [54], Preferred Reporting Items for Systematic reviews, extensions of Meta-Analyzes, Scoping Reviews (PRISMA-ScR, Data Sheet S1), and randomized clinical trials. Human and preclinical studies were included.

2.1. Step 1: Identifying the Research Question

The aim of this scoping review was to identify the role of nociceptive innervation of the TLF in musculoskeletal pain.

2.2. Step 2: Identifying Relevant Studies

A search strategy was developed using a combination of relevant keywords (Data Sheet S2). The search was conducted in June 2021 in the electronic databases of PubMed, ScienceDirect, Cochrane, and Embase. Based on the scoping review methodology, the search filters used were the following: (a) pre-clinical studies; (b) clinical trials; (c) until the year 2021; (d) full text. Additional filters used were the following: (1) Species: human and animals; (2) Language: English; (3) Sex: female and male.

Both animal models and human studies were included. A combination of DeCs descriptors in English was used: fascia, pain, and lower back pain. After excluding duplicate articles, titles and abstracts were read for later selection to read the full text. Through the search for the DeCs descriptors, we found the following numbers of articles: (a) fascia and pain, 217 articles; (b) fascia and nociceptive pain, 13 articles (all duplicates); (b) fascia and nociceptive pain and innervation (in vivo studies/ex vivo studies), 15 articles (all duplicates); (e) fascia and nociceptive pain and myofascial pain syndrome, 3 articles (a single article duplicated); (f) fascia and nociceptive pain and lower back pain, 9 articles (all duplicates).

2.3. Step 3: Study Selection

Inclusion and Exclusion Criteria

The inclusion criteria consisted of the following: (a) studies published in English; (b) complete studies (c) preclinical and clinical (in vivo and ex vivo) studies; (d) original

data studies; (e) studies involving the relationship between fascia and pain; (f) included quantification of at least one analysis of any nociceptive component of thoracolumbar fascia.

Studies were excluded if classified as the following: studies involving the relationship between fascia and proprioception, usage protocols, clinical intervention, fasciotomy, surgical procedures and medicine, practical guidelines, unpublished manuscripts, dissertations, reviews, expert comments, books and/or chapters of books, registered reports, conference proceedings.

Records screened by title and abstracts numbered 214. After reading the abstracts, 154 were excluded due to failure to meet the inclusion criteria. Fully read articles numbered 60, and of these, 48 were excluded because the content did not address the proposed theme, included interventions, or were related to fasciotomy, surgical procedures associated with the usage of medication, crural fascial, or proprioceptive innervation of facial tissue (Figure 1). In the end, two tables containing a total of 12 articles were developed: (a) Table 1—ex vivo studies and (b) Table 2—in vivo studies.

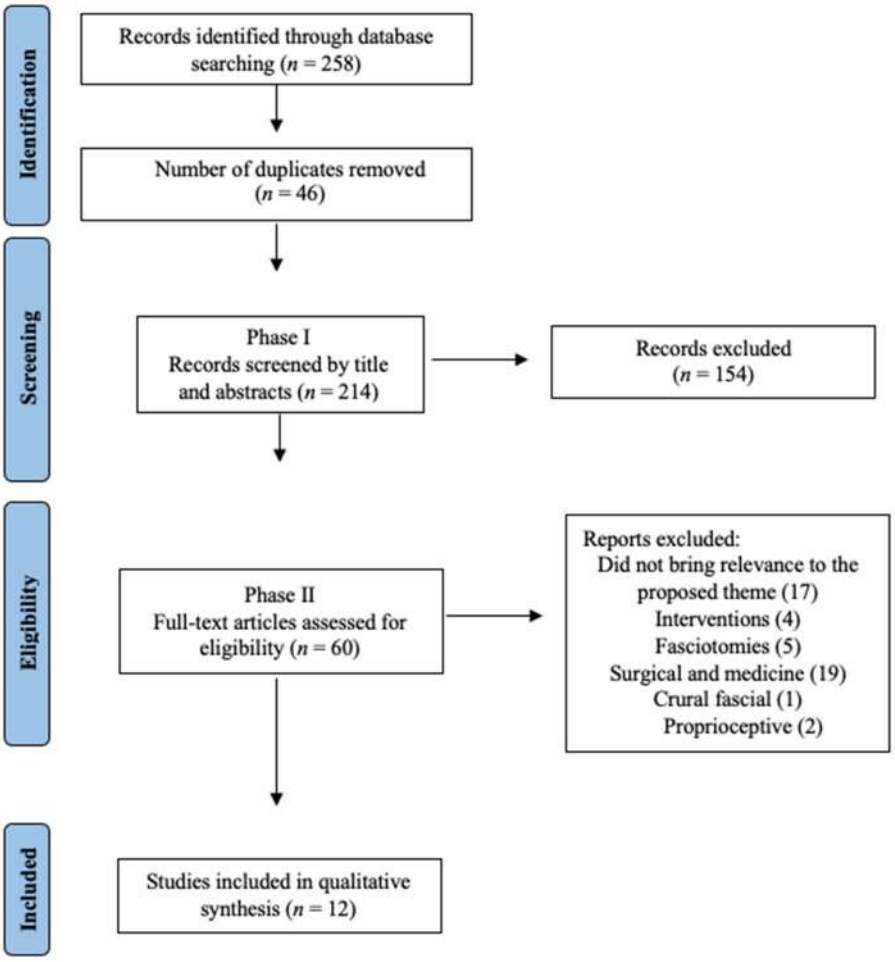

Figure 1. Flowchart diagram (file in attachment).

Table 1. Ex vivo studies.

Studies (Authors, Years)	Specie, Condition, *n*	Method	Main Findings
Corey et al., 2011 [55]	Rats, Naïve, *n* = 17	• Three-dimensional reconstructions of thick tissue sections (lower back L1–L6) • Fast Blue retrograde labeling (lower back muscle—DRG) and immunofluorescence with CGRP antibody	• 60–88% DRG cells with terminations within the collagen matrix of connective tissue in the lowr back also expressed CGRP.
Barry et al., 2015 [56]	C57Bl/6 mouse, Naïve, 4–8 per group	• Immunohistochemistry: TLF were multiple-labeled using antibodies to the pan-neuronal marker neuron-specific enolase (NSE), and CGRP and SP • Multiple-labeling immunofluorescence and retrograde axonal tracing	• The TLF contained the same proportions of nerve fiber subpopulations found in back muscles. • The TLF contained a higher density of sensory nerves, with three times more CGRP-immunoreactive fibers compared to back muscles (latissimus dorsi). However, around half of these lack SP-immunoreactivity.
Mense et al., 2016 [57]	• Rats, Naïve, *n* = 5 • Fascia inflammation—CFA, *n* = 5 • Dorsal root electrical stimulation, *n* = 4	• Immunohistochemical antibodies to CGRP, SP, and TRPV1 • Functional data Neurogenic plasma extravasation (Evans Blue)	In naïve rats, • CGRP-immunopositive fibers were found in the outer and inner layer of TLF. • SP-containing nerve fibers existed exclusively in the outer layer of TLF. In inflamed (CFA) rats, • The CGRP-immunopositive fiber length increased significantly only in the deep lamina of the posterior TLF layer • SP-positive structures were found in the same layer of TLF. In inflamed (electrical stimulation) rats, • Neurogenic plasma extravasation existed in the form of dark patches of Evans blue in the TLF
Tesarz et al., 2011 [50]	• Rats, Naïve, *n* = 8 • Specimens Humans TLF *n* = 3	• Immunohistochemical antibodies to PGP 9.5, TH, CGRP, and SP	In rats, • Fibers immunoreactive to PGP 9.5, TH, CGRP, and SP were found in the layer adjacent to the subcutaneous tissue and the superficial lamina of the posterior TLF layer. In humans, • The majority of peptidergic nerve endings were located in the subcutaneous tissue and in structures comparable with superficial and deep lamina of the posterior rat TLF layer.
Mense et al., 2019 [39]	• Rats, Naïve and Fascia inflammation—CFA, *n* = NI • Specimens Humans TLF *n* = NI	• Immunohistochemical antibodies to PGP 9.5, TH, CGRP, and SP	In rats, • Fibers immunoreactive to PGP 9.5, TH, CGRP, and SP were found in the TLF. • The inflamed fascia exhibited a higher density of CGRP-immunoreactive and SP- immunoreactive units. In humans, • Fibers immunoreactive to CGRP were the most frequent ones.

Table 1. *Cont.*

Studies (Authors, Years)	Specie, Condition, *n*	Method	Main Findings
Marpalli et al., 2021 [58]	• Specimens Humans TLF *n* = 20	• Microscopy—Morphological morphometric study	• The quantification of peripheral nerves and nociceptors were quantifiable in the deep lamina of TLF. • The thickness of TLF and number of nerve endings in the sacral level was increased compared to that of thoracic vertebral levels.
Fede et al., 2021 [59]	C57Bl/6 mouse, Naïve, *n* = 7	• Immunohistochemical: TLF were multiple-labeled using antibodies to Tyrosine Hydroxylase, S100, and PGP • Transmission electron microscopy	• The TLF presented free nerve endings and autonomic innervation.

Note: CFA—complete Freund's adjuvant; CGRP—calcitonin gene-related peptide; DRG—dorsal root ganglia; SP—substance P; TLF—thoracolumbar fascia; TRPV1—transient receptor potential vanilloid 1—TH: tyrosine hydroxylase; NI—not informed.

Table 2. In vivo studies.

Studies (Authors, Years)	Species, Condition, *n*	Method	Main Findings
Schilder et al., 2014 [42]	Healthy humans; Ultrasound-guided bolus injections of hypertonic saline into the erector spinae muscle, the thoracolumbar fascia (TLF, posterior layer), and the overlying subcutis; *n* = 6 women, *n* = 6 men	• Pressure pain threshold (algometer) • Pain distribution (two-dimensional paper form body image) • Pain quality (Pain Perception Scale, "Schmerzempfindungs-Skala" [SES])	• Hypertonic saline injected into the fascia resulted in longer pain duration and higher pain intensities than injections into subcutaneous tissue or muscle. • Pain radiation and pain affect evoked by fascia injection exceeded those of the muscle and the subcutaneous tissue. • Pain descriptors (burning, throbbing, and stinging) suggested innervation by both A- and C-fiber nociceptors.
Schilder et al., 2016 [43]	Healthy humans; Electrical stimulation with high-frequency pulses in the multifidus muscle and the overlying TLF through bipolar concentric needle electrodes placed at lumbar level (L3/L4); *n* = 8 women, *n* = 8 men	• Electrical detection threshold and pain threshold • Pain distribution (two-dimensional paper form body image) • Pain rating during HFS	Fascia vs muscle high-frequency stimulation (HFS): • Electrical pain thresholds were lower and pain ratings were higher for fascia. • For both tissues, pain ratings increased significantly. • Fascia HFS increased fascia pain ratings 2.17 times compared with control site. • Muscle HFS decreased pain sensitivity of the overlying fascia by 20%. • Potentiation by fascia HFS was similar to that of skin HFS, followed over 60 min post-HFS.

Table 2. *Cont.*

Studies (Authors, Years)	Species, Condition, *n*	Method	Main Findings
Schilder et al., 2018 [44]	Healthy humans, Electrical stimulation with high-frequency pulses in the multifidus muscle and the overlying TLF through bipolar concentric needle electrodes placed at lumbar level (L3/L4); *n* = 8 women, *n* = 8 men	• Pain quality (Pain Perception Scale, "Schmerzempfindungs-Skala" [SES])	Factor analysis of the sensory descriptors revealed the following: • Superficial thermal ("heat pain" identified by the items "burning", "scalding", and "hot") and superficial mechanical factors ("sharp pain" identified by the items "cutting", "tearing", and "stinging") were more pronounced for fascia than muscle. • Deep pain (identified by the items "beating", "throbbing", and "pounding") was more pronounced for muscle than fascia.
Hoheisel et al., 2011 [60]	Rats, Naïve, *n* = 12; Rats, Treated with CFA, *n* = 32	Systematic electrophysiological recordings were made from dorsal horn neurons in spinal (Th13–L5) to obtain information about the spinal nociceptive processing from the TLF.	In naïve rats, • 6–14% of the neurons in the spinal segments Th13–L2 had nociceptive input from the TLF. • No neurons responsive to input from the TLF were found in segments L3–L5. In inflamed (multifidus) rats, • There was a significant increase from 4% to 15% in the proportion of neurons responsive to input from the TLF. • Neurons in spinal segment L3 responded to fascia input in animals.
Hoheisel et al., 2015 [61]	Rats, Intrafascial CFA injection, *n* = 25	Extracellular recordings were made from dorsal horn neurons in the lumbar segment L3, identification of receptive fields and behavioral experiments were performed.	In inflamed (Intrafascial CFA injection) rats, • 11.1% of neurons in the spinal segment L3 received input after TLF inflammation. • Compared with control, the proportion of neurons having input from all deep somatic tissues rose from 10.8% to 33.3%. • Moreover, many neurons acquired new deep receptive fields, most of which were located in the hindlimb. • Although the pressure pain threshold of the inflamed rats did not change, they demonstrated a reduction in exploratory activity.

Note: CFA—complete Freund's adjuvant; TLF—thoracolumbar fascia; HFS—high-frequency stimulation.

2.4. Screening and Agreement

The research articles were reviewed and selected in two phases. Phase I consisted of screening titles and abstracts to include possible relevant studies and to exclude irrelevant studies. Phase II consisted of screening full texts of studies previously identified as possibly relevant to select eligible studies. Screenings in phases I and II were performed by two independent reviewers (L.S., M.A.) and any discrepancy in relation to the study's eligibility was mediated by a third reviewer (D.F.M., *n* = 2).

2.5. Step 4: Data Charting

The following data were extracted from eligible studies: (a) references; (b) animals, disease model; (c) method; (d) main results (Tables 1 and 2). The extraction parameters were defined jointly by two authors. Data extraction was performed by one author and verified by a second author to minimize any discrepancy.

2.6. Step 5: Collating, Summarizing, and Reporting the Results

The data were summarized descriptively according to the following items:

i. Preclinical: including in vivo and ex vivo studies related to nociceptive investigation of TLF.
ii. Clinical: including in vivo and ex vivo studies related to nociceptive investigation of TLF.

3. Results

3.1. Basic Numerical Analysis

The search of the database carried out on 30 June 2021 resulted in 258 articles. After the removal of duplicates, 214 articles had their titles and abstracts screened in Phase I, and those articles considered to be eligible for Phase II were screened. Fifty-eight articles were selected to be read in full, and of these, 48 were excluded due to failure to meet eligibility requirements. Thus, a total of 12 articles were included in this review, all of which were published prior to the year 2021. These 12 articles were divided into two groups: (1) ex vivo studies and (2) in vivo studies.

3.2. Ex Vivo Studies

A total of seven studies evaluated and quantified the nociceptive nerve fibers terminating within the nonspecialized connective tissues in the lower back. Specific immunohistochemistry assays included immunofluorescence (5/7), calcitonin gene-related peptide (CGRP) immunoreactivity (5/7), substance P (SP) immunoreactivity (4/7), and retrograde labeling (2/7). Species selected for ex vivo analysis included mice (2/5), rats (4/7), and humans (3/7). Anatomical structures analyzed included the TLF (7/7), lower back muscles (7/7), and DRG (2/7). Detailed information regarding the immunohistochemistry assay, species, and outcome measures utilized can be found in Table 1.

3.3. Nociceptive Innervation of TLF: Histological Evidence

A total of seven studies characterized the distribution of the nociceptive nerve fibers terminating within the TLF [39,50,55–59]. All these studies investigated whether fasciae associated with muscle are also innervated by peptidergic nociceptive sensory fibers. Collectively, these studies regarding "naïve" fascia (mice, rats, and human) reported the following: (a) 60–88% DRG cells with terminations within the collagen matrix of connective tissue in the lower back also expressed calcitonin gene-related peptide (CGRP) immunoreactivity in rats [55]; (b) The TLF contained a higher density of sensory nerves, with three times more CGRP-immunoreactive fibers compared to back muscles (latissimus dorsi); however, around half of these lacked SP-immunoreactivity in mice [56], (c) CGRP-immunopositive fibers in the outer and inner layer of TLF and SP-containing nerve fibers existed exclusively in the outer layer of TLF in rats [57]; (d) in rats, fibers immunoreactive to protein gene product (PGP) 9.5, tyrosine hydroxylase (TH), CGRP, and SP were found in the subcutaneous tissue and the superficial lamina of the posterior TLF layer, and in humans, the majority of peptidergic nerve endings were located in the subcutaneous tissue and in structures comparable with superficial lamina and deep lamina of the posterior rat TLF layer [50]. Two studies investigated nociceptive-related responses to experimental irritation of the TLF, which resulted in the following: (a) in rats with CFA injections made in the spinous processes L4 and L5, the CGRP-immunopositive fiber length increased significantly only in the inner layer of TLF and SP-positive structures were found in the deep lamina of the posterior TLF layer [57]; (b) in rats, inflammation was induced by electrically stimulating the dorsal roots L3–L6 at an intensity supramaximal for unmyelinated fibers. Specifically, SP and CGRP are known to cause plasma extravasation by increasing the permeability of capillaries close to the endings. Neurogenic plasma extravasation in the form of dark patches of Evans blue in the TLF were observed [57].

3.4. In Vivo Studies

A total of five studies evaluated and quantified nociceptive outcomes after electrical and chemical stimulation of the TLF relating to its contribution to LBP [42–44,49,50]. Of

these five studies, two investigated the role of chemical (3/5) and electrical (2/5) irritation of the TLF on measures related to nociceptive innervation of the lower back as a potential source of LBP. Specific outcomes included electrophysiological recordings from dorsal horn neurons in spinal (2/5), pressure pain threshold (algometer) (2/5), pain distribution (1/5), pain quality (1/5), and electrical detection threshold (1/5). Two studies made systematic recordings from dorsal horn neurons in the spinal cord to obtain information about the spinal nociceptive processing from the TLF in naïve rats. Species selected for in vivo analysis included rats (2/5) and humans (3/5). Anatomical site of analysis included the TLF (5/5), lower back muscles (5/5), and dorsal horn neurons in spinal (2/5). Detailed information regarding the species and outcome measures can be found in Table 2.

3.5. Nociceptive Innervation of TLF: Functional Evidence

A total of five studies evaluated the role the nociceptive input through electrical and chemical stimulation of the TLF in relation to LBP [42–44,60,61]. Of these five studies, three investigated the role of chemical irritation of the TLF on measures related to nociceptive innervation of the lower back as a potential source of LBP. These studies regarding chemical irritation of fascia (in rats and humans) reported the following: (a) in rats with bilateral complete Freund's adjuvant (CFA) [60] with injections made in the spinous processes L4 and L5 or intrafascial (L3) [61], there was a significant increase from 4% to 15% in the proportion of neurons responsive to input from the TLF and neurons in the L3 spinal segment that did not receive input from the fascia in control animals; (b) healthy volunteers received ultrasound-guided bolus injections of hypertonic saline into the erector spinae muscle, in the deep lamina of the posterior TLF layer, and the overlying subcutis. Hypertonic saline injections into the TLF resulted in longer pain duration and higher pain intensities than injections into subcutaneous tissue or muscle. Pain radiation and pain affect evoked by fascia injections exceeded those of the muscle and the subcutaneous tissue. Pain descriptors (burning, throbbing, and stinging) suggested innervation by both A- and C-fiber nociceptors [42].

Two studies [43,44] used electrical stimulation with high-frequency pulses in the multifidus muscle and the overlying TLF through bipolar concentric needle electrodes placed at lumbar level (L3/L4) to assess distinct differences between nociceptive innervation of lower back fascia and muscles in humans. These studies reported the following: (a) lower electrical pain thresholds and higher pain ratings for fascia for both tissues. Fascia high-frequency stimulation increased fascia pain ratings 2.17 times compared to control; muscle high frequency stimulation (HFS) decreased pain sensitivity of the overlying fascia by 20%; potentiation by fascia HFS was similar to that of skin HFS, followed over 60 min post-HFS [43]; (b) Factor analysis of the sensory descriptors revealed that superficial thermal and superficial mechanical factors were more pronounced for fascia than muscle, whereas deep pain was more pronounced for muscle than fascia [44].

4. Discussion

The main objective of this scoping review was to assess current knowledge regarding nociceptive innervation of the TLF to better inform future mechanistic and clinical TLF research targeting LBP treatment. The results observed here, from a collective compilation and evaluation of studies on TLF nociceptive innervation, demonstrate that rodents and humans have an important nociceptive afferent TLF innervation and that the stimulation of this structure can lead to a central sensitization process in the long term. In this sense, these findings support the idea—through neurophysiological substrates related to nociceptive innervation—that TLF may be, at least in part, the origin of LBP. Although we recognize that the sensory innervation of the TLF encompasses proprioceptive, autonomic, and nociceptive components, here, we focus on nociception as a direct cause of pain. In that regard, articles for this review were restricted to preclinical and clinical including ex vivo (n = 7) and in vivo (n = 5) studies related to nociceptive investigation of TLF.

4.1. Ex Vivo Studies

Ex vivo studies were constituted primarily of specific immunohistochemistry assays to neuropeptides [39,50,55–57]. Mice [56], rats [39,50,55–57], and humans [50,57] presented positive immunoreactivity to SP and CGRP in the TLF, a nonspecialized connective tissue in the lower back [51]. Furthermore, functional evidence confirmed the hypothesis of nociceptive innervation of TLF, since the chemical irritation of the fascia by local injection of CFA significantly increased SP- and CGRP-immunopositive fiber in the deep lamina of the posterior TLF layer. In addition, electrical stimulation of the dorsal lumbar roots at an intensity for unmyelinated fibers increased the permeability of capillaries close to the endings, causing neurogenic plasma extravasation, a phenomenon known to be caused by SP and CGRP [57]. DRG neurons traced from the collagen matrix of connective tissue in the lower back support the finding that populations of CGRP-immunoreactive fibers innervate the TLF [55,56]. Innervation density was higher in the TLF compared to muscles of the back, supporting the view that the TLF may make an under-recognized contribution to chronic back pain.

4.2. In Vivo Studies

In vivo and functional studies were constituted primarily of articles that evaluated nociceptive outcomes after chemical [42] and electrical [43,44] stimulation of the TLF relating to its contribution to LBP. In humans, the pain evoked by ultrasound-guided bolus injection of hypertonic saline [42] or electrical stimulation [43] in TLF tissue exceeded those of muscle. Furthermore, the pain after chemical stimulation of TLF was described by the patients in rather extreme terms such as cutting, tearing, and stinging, which suggests innervation by both A- and C-fiber nociceptors [42,62,63]. In contrast, muscle-derived pain was predominantly attributed to sensory qualities like throbbing and pounding [44]. It is understood that C- and A-cutaneous afferents correlate with group IV and III muscle afferents [62]. However, the fact that muscle-associated pain differs from cutaneous-associated pain strongly suggests that the neurophysiological mechanisms are not similar. Studies have suggested the term fasciatome for segmental innervation deep fascia which helps to differentiate between pain of cutaneous origin and pain of muscular origin [50,51,64]. Unlike the dermatome, which represents the portion of tissue composed of skin, hypodermis, and superficial fascia supplied by all cutaneous branches of an individual spinal nerve, the fasciatome is the portion of the deep fascia supplied by the same nerve root and organized along lines of force to emphasize the main directions of movement. When the dermatome is altered, it signals the location of pain, while the fasciatome demonstrates pain irradiation through the organization of the fascial anatomy [50,51,64]. This is evident when electrical stimulation of the muscle nerves produces only a single pain, as opposed to electrical stimulation of the cutaneous nerves which presents pain in two phases [63]. Corroborating the findings of our scoping review, it has been previously described that fascial pain quality is different, as cutaneous pain is well localized and described as stabbing, burning, or cutting, while muscle pain tends to be referred to and described as tearing, cramping, or pressing [63]. Finally, electrophysiological recordings from dorsal horn neurons in spinal cord rats showed that the nociception evoked by the injection of a chemical irritant in the lumbar spinous process increased the proportion of neurons responsive to input from TLF and neurons in the L3 spinal segment that previously did not respond to input from the fascia in naive animals [60]. Interestingly, this study also showed that most dorsal horn neurons that receive nociceptive input from the TLF are convergent and have additional input from other tissues, such as skin and lumbar muscles, at least in rats [60]. The nociceptors located in the fascia are possibly the beginning of the nociceptive pathway from the lumbar region soft tissue to the spinal dorsal horn and to other central locations from there. Since input from all soft tissues of the lower back converge onto the same dorsal horn neurons, no separate pathway from fascia to higher centers appears to exist. This may be the explanation for why a pain from the TLF is difficult to distinguish from the pain from other soft tissues of the lower back [60,61]. Hoheisel et al. (2015) [61] made an intrafascial

CFA injection in the TLF and registered dorsal horn neuron activity in the lumbar segment L3. They observed that the proportion of neurons with input from all deep somatic tissues rose from 10.8% to 33.3% when compared with control. One of the most relevant findings in animals with fasciitis was the appearance of new receptive fields in deep somatic tissues beyond the fascia, located outside the lumbar region and extending to the distal hindlimb. The appearance of new receptive fields could be a possible explanation for the spread of pain in patients with LBP.

4.3. Limitations

Limitations associated with this scoping review include selecting publications in English only and free full text publications, which could potentially reduce the number of studies being retrieved from the literature search.

4.4. Clinical Perspectives and Future Directions

Published guidelines have proposed non-pharmacological approaches such as exercise and physical therapy (massage, acupuncture, spinal manipulative therapy) as first-line treatments for lower back pain primarily due to concerns about the risk–benefit ratio of opioids and suboptimal opioid-related results in clinical trials [65–67]. A major gap in LBP research includes the contribution of musculoskeletal tissues (unspecialized muscles and connective tissues) in the lower back of the spine [68]. Although not well understood, the pathophysiology of non-specialized connective tissues, their relationship to LBP, and other conditions of chronic musculoskeletal pain can include fibrosis, chronic inflammation and neuroplastic changes, such as altered sensitivity [69–73]. Thus, the results of the present study highlight the role of connective tissue innervation in the development of lower back pain by demonstrating the presence of sensory nerve fiber endings within the collagen matrix of non-specialized connective tissue, and that structural innervation of these connective tissues is important for functional changes associated with neurogenic inflammation and persistent pain. Based on the results of this review, it is suggested that the treatment of TLF should also be considered in LBP therapeutic approaches.

Despite the recent increase in the number of basic scientific investigations describing the nociceptive innervation of TLF, this review has identified numerous areas that require further study to advance the field and deepen our understanding of the fascia approach. Although peripheral evidence exists and provides strong evidence for neurophysiological substrates of the nociceptive innervation of the fascia, there is limited evidence related to the central (supra-spinal) mechanisms involved. Future preclinical studies related to techniques aimed towards treatment (i.e., manipulation/mobilization) of TLF mimicking the clinical setting could be useful to advance knowledge and help with the treatment of musculoskeletal pain. In this sense, preclinical studies that record the results immediately after (or shortly thereafter) the delivery of fascial manipulation, long-term or longitudinal studies, and studies that investigate the physiological impact of different fascial manipulation dosage are needed. As in the study of França et al., 2020 [74], preclinical studies are just beginning to recognize and demonstrate that analgesic modulation related to fascial manipulation involves complex mechanistic interactions. Thus, preclinical studies that investigate endogenous neurological systems such as endogenous opioids [75], endocannabinoids [76], adenosinergic system [77], and/or neuroimmune contributions [74,78] are needed, and these effects may require that certain fascial manipulation dosage thresholds be achieved. Preclinical studies investigating the effects of fascial manipulation on gene expression, neurotransmitter/neuropeptide/cytokine release, mechanosensitive ion channel activation, neuroimmune response, global cortical/spinal circuit connectivity, and descending inhibition [77,78] are needed to advance the manual therapy field and deepen our understanding of fascial manipulation.

5. Conclusions

While more studies are clearly needed, findings from this review based on histological, immunohistochemical, electrophysiological, behavioral, and clinical evidence support the view that the TLF potentially plays a major role in clinical LBP, or at least makes significant contribution.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/jcm10194342/s1, Data Sheet S1: PRISMA-ScR; Data Sheet S2: search strategy.

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Abbreviations

ASICs	acid-sensing ion channels
CFA	complete Freund's adjuvant
CGRP	calcitonin gene-related peptide
DRG	dorsal root ganglia
GDNF	glial-derived neurotrophic factor
HFS	high-frequency stimulation
LBP	low back pain
MSK	musculoskeletal
NGF	nerve growth factor
NSE	neuron-specific enolase
PGP	protein gene product 9.5
SP	substance P
TH	tyrosine hydroxylase
TLF	thoracolumbar fascia
TRPA1	transient receptor potential ankyrin 1
TRPM8	transient receptor potential cation channel subfamily M member 8
TRPV1	transient receptor potential vanilloid 1
WHO	World Health Organization

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