Advances in Research

Volume 25, Issue 3, Page 266-275, 2024; Article no.AIR.116044
ISSN: 2348-0394, NLM ID: 101666096

Association between Serum Biomarkers of Muscle Damage after Isokinetic Eccentric Exercise in Trained Males and Females

Olavo João Frederico Ramos Junior [a], Isabela Ribeiro Grangeira Tavares [a], Natalia Soares Veiga [a], Gustavo Vieira de Oliveira [a,b] and Thiago Silveira Alvares [a,c++*]

[a] Nutrition and Exercise Metabolism Research Group, Multidisciplinary Center UFRJ-Macaé, Federal University, Rio de Janeiro, Macaé, Brazil.
[b] Medical Science Institute, Multidisciplinary Center UFRJ-Macaé, Federal University, Rio de Janeiro, Macaé, Brazil.
[c] Food and Nutrition Institute, Multidisciplinary Center UFRJ-Macaé, Federal University, Rio de Janeiro, Macaé, Brazil.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/AIR/2024/v25i31071

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/116044

Original Research Article

Received: 16/02/2024
Accepted: 20/04/2024
Published: 24/04/2024

ABSTRACT

Eccentric exercise is well-known to induce muscle damage, and biomarkers may be related to the magnitude of impact on muscle force and muscle soreness after exercise. However, this phenomenon still needs to be investigated in more detail. The present study aimed to analyze if a

[++] Ph.D. Adjunct Professor and Director;
**Corresponding author: E-mail: alvares@macae.ufrj.br;*

correlation between muscle force, soreness, and biomarkers after eccentric exercise exists in healthy, trained 11 males and females. Eleven volunteers with previous resistance training experience performed 6 x 10 maximal isokinetic eccentric contractions of the elbow flexors in the muscle performance laboratory up to 72 hours after exercise. Peak torque was measured by maximal voluntary isometric contractions (MVIC) and muscle soreness by visual analogic scale (VAS) before, 24h, 48h, and 72h after the isokinetic eccentric exercise protocol. A fluorescence immunoassay analyzer determined Myoglobin and C-reactive protein levels. The MVIC significantly decreased while muscle soreness increased 24h, 48h, and 72h post eccentric exercise. Myoglobin significantly increased 48h and 72h after exercise. Muscle soreness was inversely correlated with MVIC 24h, 48h, and 72h and positively correlated with myoglobin 48h and 72h after eccentric exercise. The myoglobin was not correlated with muscle force. No significant correlation between C-reactive protein and muscle soreness and MVIC was found. In conclusion, our data suggest that myoglobin could be a valuable biomarker to be assessed alongside exercise-induced muscle soreness.

Keywords: Eccentric exercise; inflammation; muscle recovery; muscle soreness; myoglobin.

ABBREVIATIONS

CRP : C-Reactive Protein
DOMS : Delayed Onset Muscle Soreness
EIMD : Exercise-Induced Muscle Damage
Mb : Myoglobin
MVIC : Maximal Voluntary Isometric Contractions
VAS ; Visual Analogic Scale

1. INTRODUCTION

Exercise-induced muscle damage (EIMD) usually occurs following a strenuous exercise involving unusual exercises and/or repetitive eccentric contraction (muscle lengthening) during exercise. Eccentric muscle contraction is a well-known phase of muscle contraction that induces more robust muscle damage [1]. Muscle damage involves myofibrillar ruptures and is associated with inflammatory response and abnormal production of reactive oxygen species (oxidative stress), resulting in muscle soreness and reduced muscle force and power after a high-intensity exercise session. In this context, inflammatory, oxidative stress, and muscle damage biomarkers assess muscle recovery after a high-intensity exercise session[2].

Several studies have investigated the effect of eccentric exercise on muscle damage over 96 hours after a single session of eccentric exercise [2–4]. It has been demonstrated that muscle force has been reduced, and muscle soreness has increased up to 48-72 hours after eccentric exercise [5–7]. Speeding up muscle recovery after exercise is important to exercise performance, given that most sports demand a high muscle performance over days, weeks, and even months.

Many studies have shown that some serum biomarkers, such as myoglobin (muscle damage biomarker) and C-reactive protein (inflammatory biomarker), increase with eccentric exercise, which is utilized as indications of muscle damage. Myoglobin, a protein in skeletal muscle, is released in the bloodstream when muscle is damaged during high-intensity exercise, typically performed by athletes[8]. Muscle damage induces an inflammatory response that can be detected by increased plasma C-reactive protein [9-10]. Myoglobin and C-reactive protein are important in assessing athletes' muscle damage and/or recovery after exercise from different perspectives (muscle damage magnitude and inflammatory response) [8–10]. Muscle swelling and soreness result from an inflammatory response when the muscle is damaged during exercise. This fact impairs muscle's ability to generate force, negatively affecting athletes' exercise performance.

Previous studies have demonstrated increased myoglobin and C-reactive protein from 24 hours to 96 hours after eccentric exercise [8–10], suggesting that myoglobin and C-reactive protein are useful serum biomarkers of muscle damage to better evaluate muscle recovery after intense exercise (i.e., eccentric exercise). In practical terms, analyzing serum biomarkers would be a faster strategy for evaluating muscle recovery after exercise. Understanding the association between myoglobin and C-reactive protein increase after eccentric exercise and muscle force (maximal voluntary contraction) recovery and muscle soreness would be essential as it might provide valuable insights for developing dietary strategies or pharmacological interventions to accelerate muscle recovery [11-14]. Furthermore, it has the potential to guide

physiologists to elaborate adequate training programs for athletes. However, it is not clear if a correlation between these serum biomarkers and muscle force and muscle soreness exists; thus, evidence needs to be shown to reinforce the utilization of myoglobin and C-reactive protein as indicative of muscle damage so that a training and/or dietary strategy can be adopted in order to improve muscle recovery in athletes. Therefore, this study investigated whether a correlation exists between serum biomarkers and muscle force and soreness over 72 h after eccentric exercise. We hypothesized that a significant correlation between muscle force declines and muscle soreness would be correlated with serum biomarkers.

2. METHODS

2.1 Participants

Eleven healthy participants (6 males), 26 ± 5 years old, with previous resistance training experience (at least three months) were recruited to participate in the study. All participants were fully informed of the nature and purpose of the investigation and gave their written consent to participate. The physical characteristics of the participants are described in Table 1. The exclusion criteria for participation in the study were any known cardiovascular, pulmonary, or metabolic diseases (i.e., asthma, diabetes *mellitus*, hypertension, dyslipidemia, smoking), upper limb injury, and/or the use of nutritional supplement (i.e., creatine, caffeine, and vitamins and minerals complexes), anabolic steroids, and anti-inflammatory drugs six months before the beginning of the study.

2.2 Experimental Design

Participants were required to come to the laboratory for five days, the first visit being baseline testing and familiarization with the eccentric exercise protocol. During the familiarization with the exercise protocol, the participants were instructed to perform minimal effort to prevent unintentional muscle damage and to ensure they did not induce an adaptative repeated bout effect [15]. One week after familiarization, the volunteers returned to the laboratory for four consecutive days (Pre-exercise, 24h, 48h, and 72h after exercise). Measures were taken in the following order for each day: 1. blood samples, 2. participant's perception of muscle pain through visual analogic scale (VAS), and 3. maximal voluntary isometric contractions (MVIC). All participants completed a food diary 24h before the first visit (i.e., familiarization) and were required to follow the same diet during the entire study to avoid the influence of food on muscle recovery. They were required to abstain from alcohol, caffeine, and heavy exercise for 72h before the experimental visit and not exercise until all analysis (72h after exercise).

Table 1. Physical characteristics of the participants

Characteristic	Value
Age (years)	26 ± 5
Weight (kg)	66.32 ± 11.57
Height (cm)	1.67 ± 0.08
BMI (kg/m^2)	23.58 ± 3.19
Resistance training experience (years)	4 ± 2

Values are expressed as mean ± SD

2.3 Exercise-Induce Muscle Damage Protocol

The participants performed a non-dominant elbow flexion and extension exercise with an isokinetic dynamometer (Humac Norm, CSMi Medical Solutions, MA, USA) in the eccentric (flexion) – concentric (flexion) mode. Each individual lay down in a supine position, with the elbow flexion-extension adapter adjusted to the semi-prone position, according to the body dimensions of each participant. The body was stabilized in the chair and strapped with Velcro to minimize movements other than elbow flexion and extension. These adjustments were recorded to be repeated accurately in each subsequent visit. The exercise movement was performed with a joint range of motion from 0° to 90°, beginning with concentric elbow flexion, followed by eccentric elbow extension. The subjects performed six sets of 10 maximal voluntary contractions at a velocity of 30°·s^{-1} in both the extension (active movement) and flexion (passive movement) phases, with a recovery period of 1 min between sets. To ensure maximal resistance throughout each repetition, verbal encouragement was given.

2.4 Maximal Voluntary Contraction Measurement

During the familiarization visit, the dynamometer (Humac Norm, CSMi Medical Systems, Inc., MA, USA) was set up for each participant, and settings were recorded to ensure that participants were in the same position for each

subsequent testing visit. To measure maximal isometric strength, participants completed 4 sets of 5 seconds MVIC at a 70º angle with 30-s rest between each contraction. The higher MVIC value recorded for the four contractions was used for statistical analysis. This procedure was repeated at 24h, 48h, and 72h after the eccentric exercise protocol.

2.5 Blood Sample Analysis

Blood was drawn from the antecubital vein, collected in EDTA-containing tubes, and immediately centrifuged at 3,000*g* for 10 min at 4 °C to separate the plasma before storage at -80 °C for subsequent analysis. Blood samples were used to analyze plasma concentrations of myoglobin (Mb) and C-reactive protein. Plasma concentrations of Mb and C-reactive protein were determined by a fluorescence immunoassay analyzer (Finecare Plus®, Celer Biotecnologia SA., Belo Horizonte, Brazil) using specific testing strips for each analysis.

2.6 Delayed Onset Muscle Soreness (DOMS) Measurement

Muscle soreness was measured before and after 24h, 48h, and 72h eccentric exercise protocol. Participants were asked to self-rate a 10- point-validated visual analog scale (VAS) indicating a line from 0 (no pain) to 10 (extreme pain)[16] during a passive elbow extension.

2.7 Statistical Analysis

An *a priori* power analysis was conducted (G*Power version 3.0.1) for a two-way repeated measure. Based on statical power (1 – β) of 0.80, an effect size of 0.25, and an overall significance level of 0.05. Analysis of variance was used to identify differences in maximal voluntary contraction, myoglobin, and perceived muscle soreness before and after 24h, 48h, and 72h of the exercise-induced muscle damage protocol. Multiple comparisons were conducted using the Bonferroni test when the F-ratios indicated a rejection of the null hypothesis. A Pearson correlation test was performed to detect correlations between muscle soreness, MVIC, Myoglobin, and C-reactive protein. Data were presented as means ± standard deviation. All analyses were performed using a commercially available statistical package (IBM SPSS Statistics version 22 for Mac, Armonk, N.Y., USA). The graphics were designed using GraphPad Prism 5.

3. RESULTS AND DISCUSSION

Table 2 shows significant differences between the blood markers, isometric muscle force, and muscle soreness before and after eccentric exercise. A significant main effect for time ($p < 0.001$) was found for MVIC. Post hoc analysis revealed a significant decrease in MVIC at 24h ($p < 0.001$), 48h ($p < 0.001$), and 72h ($p < 0.005$) after eccentric exercise compared to pre-exercise values. In contrast, a significant increase in muscle soreness was found at 24h, 48h, and 72h ($p < 0.001$).

A significant increase in plasma myoglobin ($p < 0.001$) was observed for biochemical marks after eccentric exercise. Post hoc analysis revealed a significant increase at 48h, 72h ($p < 0.002$) compared to pre-exercise values. Moreover, no significant change for C-reactive protein after eccentric exercise ($p > 0.05$) was observed.

Table 2. Blood markers, isometric muscle performance, and muscle soreness before and following exercise-induced muscle damage (EIMD)

	Pre-EIMD	24 h	48 h	72 h
Blood markers				
C-reactive protein (mg. L^{-1})	0.9±0.4	1.6±1.4	1.4±1.2	1.2±1.1
Myoglobin (ng. mL^{-1})	18.6±3.3	28.6±20.8	84.9±119.1*	97.8±130.8*
Isometric muscle performance				
MVIC (Nm)	54.4±24.7	45.9±27.0*	45.9±26.6*	48.6±26.1*
MVIC (% change)	100±0.0	82.2±20.5*	80.3±22.5*	87.9±21.4*
Muscle soreness				
DOMS (VAS)	0±0	2±2*	3±3*	3±3*

*Values are mean ± standard deviation. DOMS = Delayed Onset Muscle Soreness; MVIC = Maximal Voluntary Isometric Contraction; VAS = Visual Analogic Scale. The symbol * denotes significantly different from pre-EIMD ($p < 0.05$)*

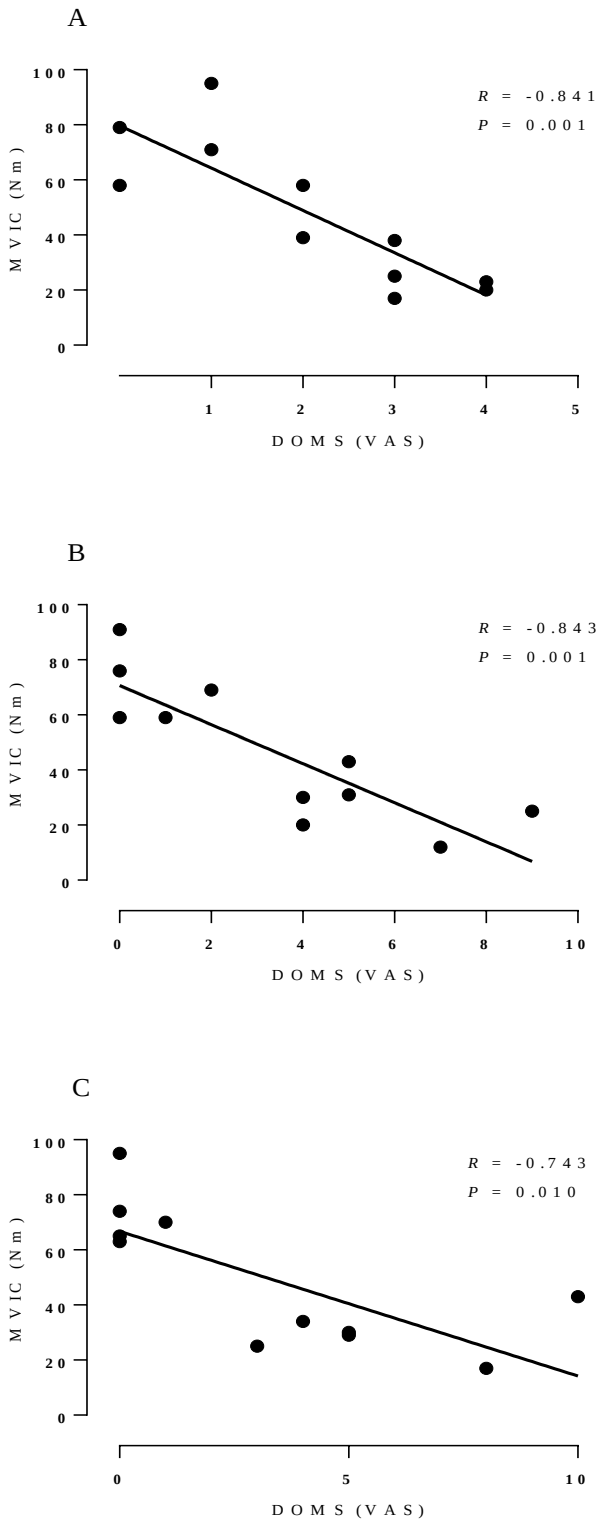

Fig. 1. Correlation between delayed-onset muscle soreness (DOMS) and maximal voluntary isometric contraction (MVIC) at 24 h (A), 48 h (B), 72 h (C) post-eccentric exercise in healthy adult individuals

Table 3. Correlations between muscle damage parameters of the participants before and following Exercise-induced muscle damage (n = 11)

Relationship	*24 h*	*48 h*	*72 h*
Between DOMS (VAS) and MVIC (Nm)			
r	-0.84	-0.84	-0.73
P	0.01**	0.01**	0.01*
Between DOMS (VAS) and Mb (ng.mL^{-1})			
r	0.29	0.83	0.89
P	0.19	0.01**	0.01**
Between MVIC (Nm) and Mb (ng.mL^{-1})			
r	-0.68	-0.33	-0.26
P	0.76	0.12	0.23
Between CRP (mg.L^{-1}) and MVIC (Nm)			
r	0	-0.03	0.03
P	1	0.99	0.87
Between CRP (mg.L^{-1}) and DOMS (VAS)			
r	-0.30	0.5	0.25
P	0.17	0.80	0.25
Between CRP (mg.L^{-1}) and Mb (ng.mL^{-1})			
r	-0.32	-0.9	-0.19
P	0.14	0.68	0.37

*MVIC = Maximal Voluntary Isometric Contraction; DOMS = Delayed Onset Muscle Soreness; VAS = Visual Analogic Scale. Myoglobin = Mb; C-reactive Protein = CRP; Statical Significance: * P < 0.05, ** P < 0.01*

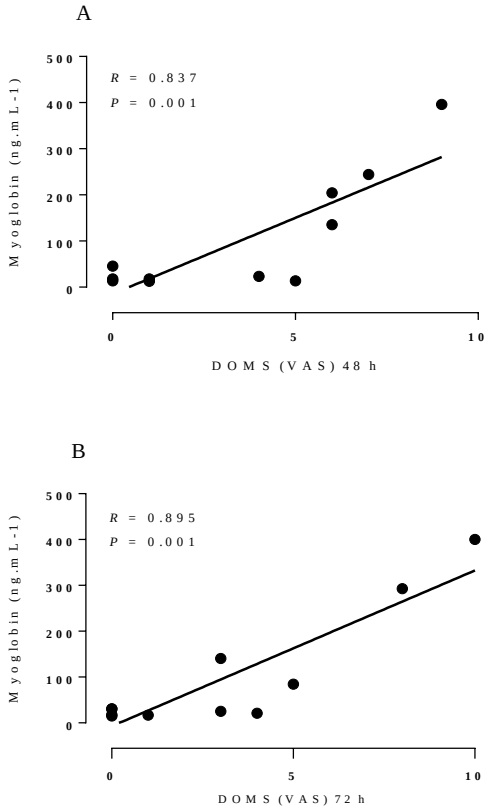

Fig. 2. Correlation between delayed-onset muscle soreness (DOMS) and myoglobin at 48 h (A), 72 h (B) post-eccentric exercise in healthy adult individuals

Table 3 shows the correlation data. A significant correlation was observed between the MVIC and muscle soreness in 24h (r = -0.841; P = 0.001), 48h (r = -0.843; P = 0.001), 72h (r = -0.734; p = 0.01) (Fig. 1 A-C) post eccentric elbow flexors protocol. A positive significance between plasma myoglobin and muscle soreness at 48h (r = 0.837; p = 0.001) and 72h (r = 0.895; p = 0.001) was found (Fig. 2 A-B). No significant correlation between myoglobin and MVIC at 24h (r = -0.680; p = 0.765), 48h (r = -0.334; p = 0.129), 72h (r = -0.265; p = 0.233) was found. No significant correlation between C-reactive protein and MVIC and muscle soreness was found in relation to pre- and post-eccentric exercise (P> 0.05).

The aim of the present study was to investigate whether a correlation exists between muscle serum biomarkers (C-reactive protein and myoglobin) and muscle force and soreness over 72h after eccentric exercise. A positive correlation between myoglobin and muscle soreness was shown, but not muscle force. Moreover, no significant correlation was observed between C-reactive protein and muscle soreness and force. We also observed a significant reduction in muscle force, as well as a significant increase in muscle soreness and myoglobin over 72h after eccentric exercise.

3.1 Muscle Function

We demonstrated a significant reduction in muscle force over 72h after eccentric exercise. In addition, a significant increase in muscle soreness was also observed after the eccentric exercise protocol at the same time course. It is well established that muscle soreness impairs exercise performance due to muscle microinjury induced by high-intensity exercise[17]. In this perspective, we observed a negative correlation between DOMS and MVC 24h, 48h, and 72h after exercise.

Our findings align with previous studies [18,19] demonstrating a decrease in muscle force associated with increased DOMS over 72 h post eccentric exercise in elbow flexor muscles. For example, Tanabe et al. (2015) observed a reduced muscle force (isometric) 24h, 48h, 72h after 1 set of 50 eccentric contractions in elbow flexor muscles in untrained young men. The authors also found a significant increase in DOMS at the same time points; it was suggested that muscle force declined after exercise due to the DOMS, which impaired muscle performance. In addition, Chen et al. [20] investigated the effect of elbow flexor eccentric contractions on DOMS and muscle force in three different intensities (10%, 50%, and 100% of MVIC) of sedentary young men. The authors found that changes in DOMS were more pronounced in those individuals who performed exercise at a high intensity (100% of MVIC); the muscle force recovery period was longer when performing a higher-intensity exercise. These findings suggested that DOMS is closely associated with muscle performance. Our study revealed a correlation between DOMS and muscle force, reinforcing that DOMS negatively affects muscle capacity to generate force. Therefore, when intense and unusual exercise is performed, higher will be muscle soreness and, consequently, the impact on the course of muscle recovery.

3.2 Muscle Damage and Muscle Function

In addition, our study also evaluated biochemical parameters commonly analyzed when investigating the effect of eccentric exercise on muscle soreness and muscle force. We found an increase in myoglobin at 48h and 72h after eccentric exercise. Typically, myoglobin is released after high-intensity exercise due to the disruption of muscle cells leaking into the extracellular space after cell membrane damage [8,10]. A previous study compared changes in myoglobin after eccentric exercise in the elbow flexor muscles among the exercises consisting of different numbers of eccentric contractions (30, 50, and 70 repetitions) in athletes (i.e., soccer, swimming, shooting, and track and field[20]. The myoglobin concentration showed a significant increase at 72h after eccentric exercise, being more pronounced in the group with more repetitions. Lavender et al. (2008) investigated changes in myoglobin after 6 sets of five eccentric contractions in elbow flexor muscles, comparing middle-aged and young men. In both groups, myoglobin concentration significantly increased in plasma 96h after exercise [21]. The myoglobin peak occurred at 72h post-exercise with no significant difference between the young and middle-aged groups.

Although a significant reduction in MVIC was observed up to 72h after eccentric exercise, we failed to show a correlation between myoglobin and muscle force. However, a significant positive correlation was observed between myoglobin and DOMS at 48h and 72h after eccentric exercise. These data suggest that myoglobin

appears to be interesting when investigating muscle soreness. The absence of a significant correlation between myoglobin and muscle force can be related to the many physiological factors that drive muscle force, such as neural and mechanical aspects of musculature.

3.3 Inflammation and Muscle Function

Furthermore, no significant change in C-reactive protein was found over 72h after eccentric exercise. A previous study has demonstrated a significant increase in serum concentration of C-reactive protein 48h after 300 maximal eccentric repetitions (30 sets of 10 repetitions) with muscle quadriceps in healthy young individuals [22]. Considering that the C-reactive protein is an acute-phase protein induced by an inflammatory response and has been used to quantify the muscle damage generated after strenuous exercise [23], it is likely that the eccentric exercise protocol utilized in the present study (6 sets of 10 repetitions) was not enough to induce a significant increase in serum concentration of C-reactive protein, given the eccentric exercise protocol utilized in the study above mentioned (300 repetitions). In contrast, in untrained individuals, there was a peak increase in C-reactive protein and DOMS at 72 h after performing eccentric exercises of elbow flexors (3 x 10 repetitions) [9]. In our study, C-reactive protein did not increase in trained individuals since the level of training of volunteers seems to impact the sensitivity of post-exercise C-reactive protein. Moreover, no significant correlation between C-reactive protein and muscle force or soreness was observed, possibly for that reason.

4. CONCLUSION

The present study demonstrated that eccentric exercise significantly reduced muscle force and increased muscle soreness and myoglobin over 72h after exercise. The myoglobin had a positive correlation with muscle soreness but not muscle force. It suggests that myoglobin could be a valuable biomarker to be assessed alongside exercise-induced muscle soreness.

CONSENT AND ETHICAL APPROVAL

All experimental procedures were performed in accordance with the ethical standards of the Declaration of Helsinki and were approved by the Institutional Ethics Committee of the Federal University of Rio de Janeiro - Macaé Campus, Rio de Janeiro, Brazil (protocol CAAE: 36846720.7.0000.5699). All individuals involved gave written informed con¬sent. The study was registered in the Brazilian Registry of Clinical Trials (ReBEC) (RBR-3bc3rnb).

DISCLAIMER

This paper is an extended version of a preprint document of the same author.
The preprint document is available in this link: https://www.researchsquare.com/article/rs-2390928/v1
[As per journal policy, preprint article can be published as a journal article, provided it is not published in any other journal]

ACKNOWLEDGEMENTS

Dr.Thiago S. Alvares, was supported by FAPERJ Young Scientist Grant Program (E-26/202.905/2019) and by National Council for Scientific and Technological Productivity Scholarship (304189/2020-0).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Markus I, Constantini K, Hoffman JR, Bartolomei S, Gepner Y. Exercise-induced muscle damage: mechanism, assessment and nutritional factors to accelerate recovery. Eur J Appl Physiol. 2021;121(4): 969-992.
DOI:10.1007/s00421-020-04566-4
2. Peake JM, Neubauer O, Gatta PAD, Nosaka K. Muscle damage and inflammation during recovery from exercise. J Appl Physiol. 2017;122(3):559-570.
DOI: 10.1152/japplphysiol.00971.2016
3. Peake JM, Neubauer XO, Della Gatta PA, Nosaka XK. REVIEW Recovery from Exercise Muscle damage and inflammation during recovery from exercise. J Appl Physiol. 2017;122:559-570.
DOI: 10.1152/japplphysiol.00971.2016.-Unac
4. Chalchat E, Gaston AF, Charlot K, et al. Appropriateness of indirect markers of muscle damage following lower limbs eccentric-biased exercises: A systematic review with meta-analysis. PLoS One. 2022;17.
DOI: 10.1371/journal.pone.0271233

5. da Silva W, Machado ÁS, Souza MA, Mello-Carpes PB, Carpes FP. Effect of green tea extract supplementation on exercise-induced delayed onset muscle soreness and muscular damage. Physiol Behav.2018;194:77-82.
DOI: 10.1016/j.physbeh.2018.05.006
6. Nieman DC, Zwetsloot KA, Simonson AJ, et al. Effects of whey and pea protein supplementation on post-eccentric exercise muscle damage: A randomized trial. Nutrients. 2020;12(8):1-14.
DOI: 10.3390/nu12082382
7. Stožer A, Vodopivc P, Bombek LK. Pathophysiology of exercise-induced muscle damage and its structural, functional, metabolic, and clinical consequences. Physiol Res. 2020;69(4): 565-598.
DOI: 10.33549/physiolres.934371
8. Saita Y, Hattori K, Hokari A, et al. Plasma myoglobin indicates muscle damage associated with acceleration/deceleration during football. Journal of Sports Medicine and Physical Fitness. 2023;63:1337-1342.
DOI: 10.23736/S0022-4707.23.15203-0
9. Phillips T, Childs AC, Dreon DM, Phinney S, Leeuwenburgh C. A Dietary Supplement Attenuates IL-6 and CRP after Eccentric Exercise in Untrained Males. Med Sci Sports Exerc. 2003;35(12):2032 -2037.
DOI:10.1249/01.MSS.0000099112.32342. 10
10. Haller N, Behringer M, Reichel T, et al. Blood-Based Biomarkers for Managing Workload in Athletes: Considerations and Recommendations for Evidence-Based Use of Established Biomarkers. Sports Medicine. 2023;53(7):1315 -1333.
DOI: 10.1007/s40279-023-01836-x
11. Owens DJ, Twist C, Cobley JN, Howatson G, Close GL. Exercise-induced muscle damage: What is it, what causes it and what are the nutritional solutions? Eur J Sport Sci. 2019;19(1):71-85.
DOI: 10.1080/17461391.2018.1505957
12. Szczyglowski MK, Ade CJ, Campbell JA, Black CD. The effects of exercise-induced muscle damage on critical torque. Eur J Appl Physiol. 2017;117(11):2225-2236.
DOI: 10.1007/s00421-017-3710-1
13. Harty PS, Cottet ML, Malloy JK, Kerksick CM. Nutritional and Supplementation Strategies to Prevent and Attenuate Exercise-Induced Muscle Damage: a Brief Review. Sports Med Open. 2019;5(1).
DOI: 10.1186/s40798-018-0176-6
14. Talebi S, Mohammadi H, Zeraattalab-Motlagh S, et al. Nutritional interventions for exercise-induced muscle damage: an umbrella review of systematic reviews and meta-analyses of randomized trials. Nutr Rev. Published. 2023:nuad078.
DOI:10.1093/nutrit/nuad078
15. Chen TC. Variability in muscle damage after eccentric exercise and the repeated bout effect. Res Q Exerc Sport. 2006;77 (3):362-371.
doi:10.1080/02701367.2006.10599370
16. Carlsson AM. *Assessment of Chronic Pain. I. Aspects of the Reliability and Validity of the Visual Analogue Scale*. Vol 16. Elsevier Biomedical Press; 1983.
17. Heiss R, Lutter C, Freiwald J, et al. Advances in Delayed-Onset Muscle Soreness (DOMS) - Part II: Treatment and Prevention. *Sportverletzung-Sportschaden*. 2019;33(1):21-29.
DOI: 10.1055/a-0810-3516
18. Tanabe Y, Maeda S, Akazawa N, et al. Attenuation of indirect markers of eccentric exercise-induced muscle damage by curcumin. Eur J Appl Physiol. 2015;115(9): 1949-1957.
DOI: 10.1007/s00421-015-3170-4
19. Chen TC, Huang GL, Hsieh CC, et al. Comparison among three different intensities of eccentric contractions of the elbow flexors resulting in the same strength loss at one day post-exercise for changes in indirect muscle damage markers. Eur J Appl Physiol. 2020;120(1): 267-279.
DOI: 10.1007/s00421-019-04272-w
20. Chen TC, Nosaka K. Effects of number of eccentric muscle actions on first and second bouts of eccentric exercise of the elbow flexors. J Sci Med Sport. 2006;9(1-2):57-66.
DOI: 10.1016/j.jsams.2006.03.012
21. Lavender AP, Nosaka K. Changes in markers of muscle damage of middle-aged and young men following eccentric exercise of the elbow flexors. J Sci Med Sport. 2008;11(2):124-131.
DOI: 10.1016/j.jsams.2006.11.004
22. Paulsen G, Benestad HB, Strøm-Gundersen I, Mørkrid L, Lappegård KT, Raastad T. Delayed leukocytosis and cytokine response to high-force eccentric

exercise. Med Sci Sports Exerc. 2005;37 (11):1877-1883.
DOI:10.1249/01.mss.0000177064.65927.98

23. Fedewa MV, Hathaway ED, Ward-Ritacco CL. Effect of exercise training on C reactive protein: A systematic review and meta-Analysis of randomised and non-randomised controlled trials. Br J Sports Med. 2017;51(8):670-676.
DOI: 10.1136/bjsports-2016-095999

Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/116044