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Correlation of Delayed Onset Muscle Soreness and Inflammation Post-exercise Induced Muscle Damage

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Abstract

BACKGROUND: Delayed onset muscle soreness (DOMS) is a common injury resulting from abnormal intensive training in athletes, mainly the result of training involving eccentric contractions.

AIM: The aim of this study was to determine the correlation between the incidence of DOMS and high mobility group box 1 (HMGB1) as a marker of the occurrence of inflammation post-exercise induces muscle damaged.

METHODS: Thirty male recreational students of Sports Science Department, Universitas Negeri Surabaya who met all inclusion and exclusion criteria participated in this study. Participants completed a muscle damaging exercise which consists of a 10 × 10 drop jump (DRP) and a bout of 40 × 15 m sprints with a 5 m deceleration zone (SPR) to obtain a muscle damage effect. DOMS and HMGB1 were carry out 1 h before the exercise, 12 h after the exercise, 24 h after the exercise, and 48 h after the exercise.

RESULTS: The result showed that there was a significant correlation (r = 0.935, sig < 0.05) between DOMS and HMGB1 as a predictor of inflammation. The participants that were given exercise induced muscle damage (EIMD) eccentric exercise (DRP and SPR) showed the occurrence of DOMS and increasing of HMGB1. The result also showed that there was a correlation between DOMS and HMGB1.

CONCLUSION: This study concluded that there was a correlation between DOMS and HMGB1 as a marker of inflammation as the result of the eccentric exercise of the EIMD.

Introduction

Unaccustomed eccentric muscle contraction exercise to exhaustive exercise could lead to muscle damage and soreness on and several days after. This condition is called delayed onset muscle soreness (DOMS). This discomfort pain sensation of DOMS could occur 1–2 days after exercise and be held for several days (4–5 days). The intensity of the pain sensation depended on the training workload with dominant eccentric muscle contraction. DOMS has some difference with acute pain that could occur shortly after exercise, the difference is in the presence of delayed pain sensation. DOMS pain usually occurs after a painless period (12–24 h after) and will peak at 24–72 h and it will disappear within 7 days [1]. Everyone may have experienced the sensation of DOMS several times, especially after doing exercise or training for the first time after a long period of rest. This is a common result of abnormally intense exercise, especially if the exercise involved involves eccentric contraction (EC) [2]. Athletes who exercise every day will also experience DOMS when they get new types of exercises or skills.

The senseless pain sensation occurrences at the start of this period make DOMS a little mysterious and are still being debated. The most typical symptom of DOMS is tenderness and pain when the muscle is moved, both are types of mechanical hyperalgesia and are usually painless at rest [3]. DOMS can impair athletes athletic performance and DOMS can cause further debilitating and chronic injury [4] and chronic pain, and also hyperalgesia with altered central nervous system plasticity. DOMS injury is associated with a reduction in maximum strength and range of motion. This reduction is thought to be related to micro disruption of the intracellular structure of the muscle fibers [5].

The previous studies explained the inferred mechanism that causes DOMS, one of them explained that EC of muscle fibers places a stretch on the sarcomere to the point at which the myofilaments may experience sarcomere strain, or damage referred to as exercise-induced DOMS [6], but the primary mechanism is currently considered to be the ultrastructural damage of muscle cells due to unfamiliar sporting activities or eccentric exercise, which leads to further protein degradation, apoptosis, and local inflammatory response [7]. Abnormal exercise consisting of eccentric muscle contraction (i.e., lengthening) often results in muscle damage characterized by ultrastructural changes in muscle tissue, clinical signs, and other

symptoms (e.g., decreased muscle strength and range of motion, increased muscle pain and swelling, and myocellular efflux) [8].

Indicate that exercise can cause muscle damage is that there is a process of lengthening and stretching of the muscle after isometric contraction, even at low-intensity exercise [9]. The state of metabolic stress and mechanical stress that occurs during exercise is thought to be the cause of muscle damage [10]. However, although DOMS is also a common symptom of muscle damage, the precise mechanism that has responsible for DOMS remains somewhat uncertain. It is generally believed that myofiber microtrauma and subsequent inflammation became the cause of DOMS, in contradiction, mechanical hyperalgesia occurs in rat muscle 1–3 days after eccentric muscle contraction, without obvious microscopic damage to the muscle or signs of inflammation [11]. Therefore, it can be said that muscle damage that occurs after exercise will cause inflammation. Inflammation is a biological response of the immune system that prevents, limits, and repairs damage by attacking endogenous pathogens or biomolecules. Although acute inflammation is a transient and beneficial inflammatory response to the organism, persistent inflammatory responses are associated with tissue dysfunction and pathology [12]. In this regard, high mobility group box 1 (HMGB1) was initially identified as a highly conserved non-histone DNA-binding factor and proved to be a potent mediator in inflammatory disease [13], excessive amounts of extracellular HMGB1, which die after cell death or through active secretion inflammation [14]. Excessive muscle cell damage due to strenuous exercise will trigger high extracellular HMGB1 secretion, which will then lead to inflammation. HMGB1 is a mediator of systemic inflammation in sepsis and trauma. HMGB1 is a mediator of inflammation in sepsis and trauma so it can be used as a biomarker in many diseases including inflammation [15]; therefore, HMGB1 is an indication of inflammation due to post-exercise muscle damage.

Based on these conditions, the purpose of this study was to determine the correlation between DOMS and HMGB1 as a marker of inflammation due to eccentric exercise (exercise-induced muscle damage [EIMD]). This study aimed to investigate the relationship between pain sensation as measured using DOMS and the occurrence of inflammation as shown by the concentration of HMGB1 as an inflammatory mediator post-EIMD in students of the Sports Science Department, Universitas Negeri Surabaya.

Materials and Methods

Thirty male recreational students of Sports Science Department, Universitas Negeri Surabaya, who met inclusion criteria (healthy, had a normal body Mass Index, non-smoker) and exclusion criteria (in drugs treatment, consume chemical drugs, and any supplements) participated in this study. In addition, these participants were not allowed to carry out any recovery programs such as massage or cryotherapy. All participants had a low risk of bias. All participants have filled out their agreement through informed consent and have filled out a questionnaire to determine the condition of blood pressure, the presence of heart disorders, diabetes, and the period of treatment. All participants have been briefed beforehand about the study and the risks that may occur. The study was carried out in May 2022 in Surabaya, the muscle soreness (DOMS) was measured in Universitas Negeri Surabaya, while blood serum data were measured at the Institute of Tropic Disease and International Research Center Laboratory, Universitas Airlangga Indonesia to obtain HMGB1 concentration data.

This was an experimental study with 30 participants in one group. This study was carried out for 1 month with an initial screening on the 1st day to determine the condition of the participants. All participants were not allowed to carry out exercise or strenuous physical activity for 30 days until the end of this study. On the 30th day, after finishing their 15 min of warming up, the participants completed 1-min interval training in both of 10 × 10 drop jump (DRP) and a bout of 40 × 15 m sprints with a 5 m deceleration zone (SPR) to obtain a muscle damage effect (EIMD).

The muscle soreness of DOMS was assessed using Visual Analog Scale (VAS) [16], [17] method. This VAS method has been used as a valid and reliable measurement for determining the intensity of human pain [18]. The VAS consisted of a 10-cm line with anchored at the number zero as “no pain” at the left end, and at the right end, there was the number ten as “most severe pain”. The VAS that felt by the participants were focused on the leg muscles of the participants. The participants were asked to fill out a questionnaire containing the VAS score scale and then mark “x” at the scale on the VAS, the investigator then measured from the no soreness at all end to the “x” (to the nearest 0.1 cm).

HMGB1 is inflammation marker due to the EIMD. Excessive muscle cell damage due to strenuous exercise will trigger high extracellular HMGB1 secretion, which will then lead to inflammation. HMGB1 is a mediator of systemic inflammation in sepsis and trauma. Measurement of HMGB1 concentration was carried out using the enzyme-linked immunosorbent assay (ELISA) technique according to the manufacturer’s instructions included with the product (HMGB1 ELISA Kit II; Abbexa). Examination of HMGB1 serum levels was carried out at the Institute of Tropic Disease and International Research Center Laboratory, Universitas Airlangga Indonesia. Serum levels of HMGB1 were checked using the ELISA KIT IBL technique, with the

Sandwich Indirect Capture Re Capture method. Both VAS and blood samples (HMGB1) were taken 1 h before the exercise, 12 h after, 24 h after, and 48 h after the exercise (EIMD).

The collected DOMS and HMGB1 data were numerical data from the VAS instrument with a scale of 1 (no pain) to 100 (severe pain) and also data on HMGB1 concentration levels (pg/mL), each of which is measured 1 h before the exercise, 12 h after, 24 h after, and 48 h after EIMD, then the collected data were analyzed statistically using SPSS 23.

The statistical analysis used was a two-way analysis of variance to represent the significance of the data. If the time variable has an effect, then it is continued with a multiple comparison test using a Bonferroni adjustment. Analysis of the correlation between data using the Pearson correlation coefficient. The level of statistical significance was set at $p < 0.05$, then the data were presented in the form of means ± standard deviation (SD). A normality test was previously performed using the Kolmogorov–Smirnov to determine whether the data came from a normal distribution.

Results and Discussion

Respondent characteristic

Several 30 with mean age of 17.80-year-old (SD ± 0.99655) male students of Sports Science Department, Universitas Negeri Surabaya were willing to become the respondent and participate in this study. Another characteristic gained from this study is shown in Table 1.

Table 1: Respondent characteristic

Variable	Age	Weight	Height	BMI
N	30	30	30	30
Min	18.00	154.00	53.00	19.72
Max	20.00	177.00	72.00	25.39
Mean	18.80	164.20	60.93	22.617
Standard deviation	0.99655	5.248	4.593	1.616

BMI: Body mass index

DOMS

Visual analog scale (VAS) [16] with 10-cm line (0 = “No pain” at the left end, and 10 = “Most severe pain” at the right) was used to determine the development of muscle soreness (DOMS) post-EIMD. The muscle soreness was carried out 1-h before, 12-h post, 24-h post, and 48-h post-EIMD, with 1-h before as baseline. The descriptive statistic of the DOMS changes is shown in Table 2.

Based on Table 2 above, it shows that DOMS sensation using VAS is felt by participants, both at 12-h, 24-h, and 48-h post-EIMD. The highest of DOMS value occurring at 24-h post-EIMD with mean value 3.84 (SD ± 0.29).

Table 2: DOMS descriptive statistics

DOMS	1 h Pre EIMD	12-h Post EIMD	24-h Post EIMD	48-h Post EIMD
N	30	30	30	30
Min	0.00	1.00	3.20	2.90
Max	0.00	1.50	4.30	4.60
Mean	0.00	1.27	3.84	3.75
Standard deviation	0.00	0.13	0.29	0.54

DOMS: Delayed onset muscle soreness, EIMD: Exercise-induced muscle damage.

Normality test in this study is needed as an assumption or condition for every parametric test. The result of normality test using Kolmogorov–Smirnov of the DOMS showed that the value of Kolmogorov–Smirnov for DOMS at the three periods which are 12-h post, 24-h, and 48 h post-EIMD has significant value of 0.104, 0.200, and 0.200 (sig >0.05), it can be then that data were normally distributed (Table 3).

Table 3: DOMS normality test

DOMS	1h Pre EIMD	12-h Post EIMD	24-h Post EIMD	48-h Post EIMD
Statistic		0.0.15	0.12	0.12
Df	30	30	30	30
Sig		0.104	0.200	0.200

Kolmogorov–Smirnov. DOMS: Delayed onset muscle soreness, EIMD: Exercise-induced muscle damage.

DOMS appeared and developed 12 h after the exercise, then increased at 24 h after the exercise, and still developed at 48 h after the exercise, compared to before the exercise (pre), with a significance level (sig < 0.01). The pain progression rate (DOMS) is shown in Figure 1.

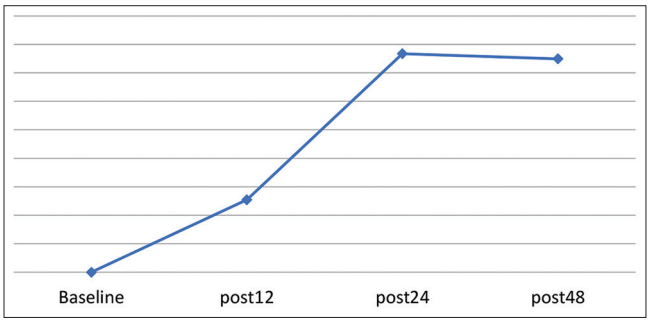

Figure 1: DOMS pain progression from 12 h to 48 h as measured in leg muscles using the visual analog scale

HMGB1 as a marker of inflammation

HMGB1 was used to measure the occurrence of inflammation post EIMD. Plasma blood samples were taken after the participants filled out the VAS questionnaire with was carried out 1-h before, 12-h post, 24-h post, and 48-h post-EIMD, with 1-h before as baseline. The descriptive statistic of the DOMS changes is shown in Table 2.

The measure is used from the table above (Table 4) to access the change of the HMGB1 as inflammation maker, and it shows that there were HMGB1 plasma concentrations changes at 12-h, 24-h, and 48-h post-EIMD. The highest of HMGB1 value occurring at 24-h post-EIMD with mean value 5.65 ng/mL (SD ± 0.17).

Table 4: HMGB1 descriptive statistics

HMGB1	1 h Pre-EIMD	12-h Post-EIMD	24-h Post-EIMD	48-h Post-EIMD
N	30	30	30	30
Min	1.00	2.33	5.33	4.72
Max	1.85	3.34	5.96	6.28
Mean	1.45	2.80	5.65	5.54
Standard deviation	0.25	0.26	0.17	0.48

HMGB1: High mobility group box 1, EIMD: Exercise-induced muscle damage.

The result of normality test using Kolmogorov–Smirnov of the HMGB1 showed (Table 5) that the HMGB1 value at the three periods which are 12-h post, 24-h, and 48-h post-EIMD has significant value of 0.177, 0.112, 0.195, and 0.165 (sig >0.05), it can be then that data were normally distributed.

Table 5: HMGB1 normality test

HMGB1	1-h Pre-EIMD	12-h Post-EIMD	24-h Post-EIMD	48-h Post-EIMD
Statistic	0.129	0.134	0.123	0.107
df	30	30	30	30
Sig	0.200	0.182	0.200	0.200

Kolmogorov–Smirnov. HMGB1: High mobility group box 1, EIMD: Exercise-induced muscle damage.

Inflammation that occurs is measured using HMGB1 as a marker of increase in the event of tissue damage

HMGB1 concentrations appeared and developed 12 h after the exercise, then increased 24 h after the exercise, and still developed at 48 h after the exercise, compared to before the exercise (pre), with a significance level (sig <0.01). The development of HMGB1 concentration is shown in Figure 2.

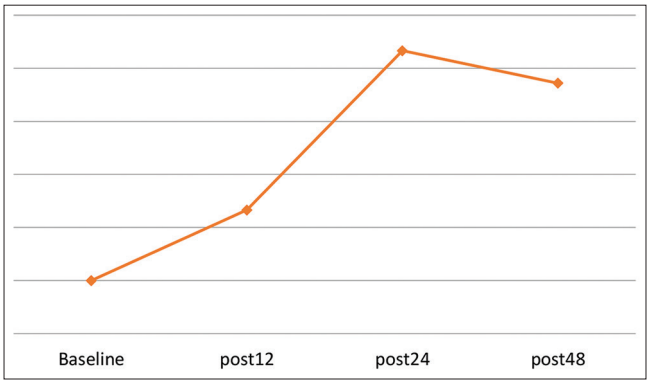

Figure 2: Inflammation progression from 12 h to 48 h as measured in leg muscles using HMGB1

Correlation between pain (DOMS) and HMGB1 as a marker of inflammation

Since the data were normally distributed (Tables 3 and 5), then statistical analysis was using the Pearson correlation coefficient to measure of the correlation between DOMS and HMGB1. The result of the correlation between the level of muscle pain measured using DOMS and an inflammatory state characterized by an increase in the HMGB1 marker in participants is explained as follows.

The results of the correlation test using Pearson's correlation coefficient showed that there was a positive correlation between increased pain sensation (DOMS) and tissue inflammatory conditions characterized by an increase in HMGB1 (r = 0.907, sig <0.05), while the correlation level was in the "strong" category, with thus it can be said that there is a strong positive correlation between the sensation of pain in the muscles and tissue inflammation due to the implementing DRP and SPR (EIMD) (Tables 6 and 7).

Based on the results that have been presented above, the pain sensation in subjects appeared 12 h after the exercise and then developed at 24–48 h after the training (sig <0.05) when compared to before the exercise, DOMS appeared in the 1st day until it reaches its peak on the 3rd day, and will decrease on the 4th day [19]. This study also noted that there was muscle damage with inflammation. Intense exercise causes a significant release of inflammatory cytokines and free radicals from activated leukocytes, causing muscle, and tissue damage [20]. Exercise-induced muscle damage and inflammation have been discussed in many studies [21], [22]. In this study, the inflammation was evidenced by an increase in the concentration of HMGB1 as a marker of inflammation. HMGB1 is an alarm in that responds to cellular stress or damage by modulating the inflammatory response. The concentration of HMGB1 increased at 12-h post-EIMD and developed 24 h, and 48 h after post-EIMD (sig <0.05) among all the participants (Figure 3). Previous studies have investigated the relationship between the level of DOMS and the occurrence of muscle damage, but these studies also have different results [23], [24]. The results corroborate previous research allegations that DOMS pain has a positive correlation with inflammation due to muscle damage, which is shown by an increase in HMGB1 after post-EIMD (r = 907, sig <0.05).

Physical activity, especially high-intensity eccentric muscle contractions, results in exercise-induced muscle damage (EIMD). Muscle fibers damage and inflammatory response due to EIMD would affect exercise performance [21], [25]. Besides that, there are general training programs provided, such as interval training with movements dominated by eccentric movements. These eccentric movements especially eccentric movements with high will provide an opportunity for DOMS [26]. Based on field observations, it was found that students had only experienced DOMS in the early stages of their practice, especially after stopping training for a period of time or having new training program. DOMS is associated

Table 6: Correlation between DOMS and HMGB1 using Pearson correlation each time

Variable	Pre		Post-12		Post-24		Post-48	
	Pearson correlation	Sig (2-tailed)	Pearson correlation	Sig (2-tailed)	Pearson correlation	Sig (2-tailed)	Pearson correlation	Sig (2-tailed)
N=30								
DOMS–HMGB1	-	-	0.468	0.009	0.609	0.000	0.918	0.000

DOMS: Delayed onset muscle soreness, HMGB1: High mobility group box 1.

Table 7: Correlation between DOMS and HMGB1 using Pearson Correlation overall

Variable	Pearson correlation	Sig (2-tailed)
DOMS–HMGB1	0.907	0.000

DOMS: Delayed onset muscle soreness, HMGB1: High mobility group box 1.

with microtrauma of connective and contractile tissues resulting from high tension forces that occur during the eccentric phase of exercise [27]. Concentric muscle contraction does not cause exercise-induced muscle damage, but exercise-induced muscle damage is clear after isometric contraction of long muscle lengths and eccentric muscle contraction, even at low intensity [28]. High-strength eccentric muscle contractions can cause delayed onset muscle pain (DOMS), prolonged loss of muscle strength, decreased range of motion, muscle swelling, and increased muscle protein in the blood. High-strength eccentric muscle contractions at ultrastructural levels of Z-line flow and myofibrillar disturbances have been considered evidence of muscle damage [10].

Figure 3: Development of DOMS and HMGB1 from 12 h to 48 h

However, DOMS can be a symptom of muscle damage, and the precise cause of DOMS is not known. One hypothesis is that mechanical hyperplasia tested on rats 1–3 days after an exercise involving eccentric muscles has not found any obvious microscopic damage to the muscles or signs of inflammation. This reduces the evidence that there is a correlation between the incidence of DOMS and inflammation. However, different assumptions suggest that muscle inflammation following exercise-induced muscle damage is sometimes considered a detrimental process associated with tissue damage, pain, and delayed recovery [29]. As described, eccentric exercise induces greater muscle breakdown and negative functional consequences in healthy nave muscles than other types of exercise. The mechanical changes and metabolic stress associated with exercise-induced muscle damage stimulate various cell types comprising skeletal muscle to initiate subsequent tissue repair and remodeling [30]. The mechanisms of muscle damage and exercise-induced inflammation have been discussed in the previous studies [31], [32], [33]. High-intensity eccentric muscle contractions induce exercise-induced muscle damage leading to an inflammatory response. However, in general, it can be said that there is indeed a correlation between DOMS and HMGB1 as a marker of inflammation. HMGB1 is actively released from immune cells such as macrophages, monocytes, NK cells, dendritic cells, endothelial cells, and platelets, It is also passively released from necrotic or damaged cells [34]. Both mechanisms can induce the release of significant amounts of extracellular HMGB1. Apoptotic cells release significantly less HMGB1 compared to necrotic cells, whereas macrophage uptake into apoptotic cells results in significant HMGB1 [35]. As an inflammation marker, HMGB1 generated by cytotoxicity activates innate immunity. This response is qualitatively indistinguishable from the response activated by infectious injury. HMGB1 activates these responses by signaling through the same receptor family activated by exogenous agents [36].

Unfortunately, due to the occurrence of inflammation in this study using HMGB1 as an inflammation marker after exercise, it remains unclear whether the exercise causes inflammation. The proof of muscle inflammation needs other cytological markers and muscle biopsy. This is a potential avenue for the future research.

Conclusions

Based on the results obtained above that there is a positive correlation between DOMS and HMGB1 as an inflammation marker, so it can be a driving force that the DOMS pain sensation that occurs after exercise has a close relationship with the incidence of inflammation.

Ethical Approval

This study protocol is already approved by the ethical committee of the Faculty of Sports Science Universitas Negeri Surabaya Indonesia 2022

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