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REVIEW ARTICLES

Effect of Caffeine Ingestion Before or After Muscle Damage on Delayed Onset Muscle Soreness: A Meta-Analysis of Randomized Controlled Trials

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Abstract

Objective: The present study aimed to conduct a meta-analysis based on available randomized controlled trial data to evaluate the effect of pre- or post-exercise caffeine ingestion on pain in individuals with Delayed onset muscle soreness. Methods: PubMed, Web of Science, Scopus, and SPORTDiscus databases were systematically searched (from inception to December 2023) to identify randomized controlled trials evaluating the effectiveness of caffeine on muscle pain before and after exercise damage. Visual analog scale was determined as the outcome measure. To compare the means and calculate the overall effect size "Cohen's d" coefficient was used. Cochran Q test and I^2 statistics were used to evaluate heterogeneity between studies. Results: Eight randomized controlled trials were analyzed as part of the meta-analysis. 5-6 mg/kg caffeine did not significantly reduce visual analog scale at 24 hours when ingested pre-damage ([Standardized Mean Difference (SMD) = -0,022, p=0,920, I^2 : 0%]), and VAS at 24, 48, and 72 hours when caffeine was used post-damage ([SMD = -0,568, p=0,135, I^2 : 75,89%], [SMD = -0,169, p=0,747, I^2 : 78,61%], [SMD = -0,181, p=0,523, I^2 : 2,78%], respectively). Conclusion: Consuming 5-6 mg/kg of caffeine before or after muscle damage is not sufficient to reduce delayed onset muscle soreness related muscle pain. The potential effectiveness of 3mg/kg caffeine in preventing or reducing delayed onset muscle soreness pain seems promising. More studies are needed to evaluate caffeine at different doses and periods.

Keywords: *caffeine, muscle pain, muscle soreness, visual analog scale, meta-analysis*

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Introduction

Delayed onset muscle soreness (DOMS) commonly develops following repeated high-intensity eccentric muscle contractions or participation in unfamiliar exercises. DOMS shows symptoms like pain, muscle and joint stiffness, muscle tenderness, swelling, decrease in muscle strength, and decrease in exercise capacity for up to 1 week (Lewis et al., 2012). One of the most commonly accepted explanations for exercise-induced muscle damage is the substantial mechanical stress exerted on muscle myofibrils during eccentric contractions and changes in metabolic activities leading to loss of cellular homeostasis induced by exercise (Clarkson & Sayers, 1999).

DOMS is considered a grade 0 muscle injury according to the British athletics muscle injury classification and is frequently seen in both elite and amateur athletes (Cheung et al., 2003; Pollock et al., 2014). Treatments such as non-steroidal anti-inflammatory, cold water immersion, stretching, massage, exercise, therapeutic ultrasound, acupuncture, and electrical stimulation have limited effectiveness on muscle pain (Cheung et al., 2003; Hübscher et al., 2008). In addition to these interventions, dietary supplements such as caffeine (Hurley et al., 2013) and ginger (Matsumura et al., 2015) which have anti-inflammatory actions, are used for the treatment of DOMS. Caffeine has been shown to increase IL-10 levels during the inflammation process induced by exercise and to support the anti-inflammatory response by reducing oxidative stress. (Tauler et al., 2013, 2016). Caffeine acts on the nervous system by blocking central adenosine A2B receptors and afferent peripheral sensory pathways A2A (Sawynok, 1998). This action can alter pain intensity and may serve as a helpful adjunct in managing both pain and headaches (Derry et al., 2014). Pre-exercise caffeine ingestion decreases the perception of pain, reduces the degree of perceived exertion, and increases exercise capacity (Doherty et al., 2004). Post-exercise caffeine ingestion increases muscle glucose levels, Calcium2+/calmodulin-dependent protein kinase phosphorylation, new glycogen synthesis rate and glycogen accumulation (Pedersen et al., 2008). Also post-exercise caffeine intake has been reported to delay autonomic recovery by causing increased sympathetic nerve activity (Bunsawat et al., 2015).

Literature review reveals several randomized controlled studies that have investigated the impact of caffeine on DOMS-related pain, with varying findings (Al-Nawaiseh et al., 2022; Chen et al., 2019; Hurley et al., 2013; Maridakis et al., 2007; Santos-Mariano et al., 2019). Some results showed that caffeine intake leads to significantly lower pain levels in the following days compared to placebo (Hurley et al., 2013; Maridakis et al., 2007). In contrast, some studies found caffeine ineffective on pain scores in DOMS (Al-Nawaiseh et al., 2022; Santos-Mariano et al., 2019). Recently, an important meta-analysis study evaluated the effects of caffeine on DOMS (Muljadi et al., 2021). Despite the potential differences in caffeine's effects when used before or after exercise, this meta-analysis analyzed studies without making a distinction between caffeine use before or after exercise (Muljadi et al., 2021).

This study aimed to perform a meta-analysis using data from existing randomized controlled trials to more clearly assess the impact of pre- or post-exercise caffeine consumption on pain in patients with DOMS.

Methods

This meta-analysis was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Literature Search Strategy

Muscle pain associated with DOMS was evaluated by conducting a literature search using electronic databases such as PubMed, Scopus, Web of Science, and SPORTDiscus to identify relevant articles assessing the impact of caffeine supplementation. The database search was performed from the earliest date to December 2023 without language filtration. The following keywords were used without any automatic filters to find the relevant articles: (caffeine) AND ((delayed onset muscle soreness) OR (DOMS) OR (muscle damage) OR (exercise-induced muscle damage) OR (EIMD) OR (muscle soreness)) AND ((VAS) OR (visual analog scale) OR (pain)).

Inclusion and Exclusion Criteria

Quasi-randomized or randomized and controlled trials published in English that used a crossover or parallel design were included in this meta-analysis. Inclusion criterias were: (1) studies compared caffeine with a placebo pre- or post exercise-induced muscle damage; (2) studies used a protocol designed to exercise-induce muscle damage (EIMD); (3) studies included in the analysis reported at least one measure of muscle soreness index following exercise-induced muscle damage, assessed at baseline and again at 24, 48, and/or 72 hours post-exercise. Exclusion criterias were: (1) studies without a control group; (2) studies used drugs, other supplements, and diet; (3) participants of the studies having any metabolic, or musculoskeletal disorders; (4) animal studies, case reports, letters to the editor, book chapters and reviews.

Study Selection

Two independent reviewers (EA and CK) performed the literature search and scanned the titles, abstracts, and identifiers of the studies. Studies meeting the inclusion criterias were identified and evaluated as full texts. Any disagreements were resolved through consultation with a third reviewer (UŞ). Figure 1 illustrates the flow diagram of the literature search process.

Data Extraction

The details of the studies, participants' characteristics, and the results were extracted from published data. Data were extracted from the graphs using WebPlotDigitizer 4.6 (California, USA, 2022) (Drevon et al., 2017) when the articles did not provide data and the authors did not give an answer to any communication requests.

Risk of Bias Assessment

Two reviewers (EA and UŞ) used Version 2 of the Cochrane Risk of Bias Tool for randomized trials (ROB 2) (Sterne et al., 2019) to assess the risk of bias, focusing on five domains: the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of reported results. An independent researcher was consulted in the case of any disagreement. The overall assessment consisted of three ratings: high risk of bias, some concerns, and low risk of bias. The risk of bias summary and risk of bias graph are shown in Figure 2.

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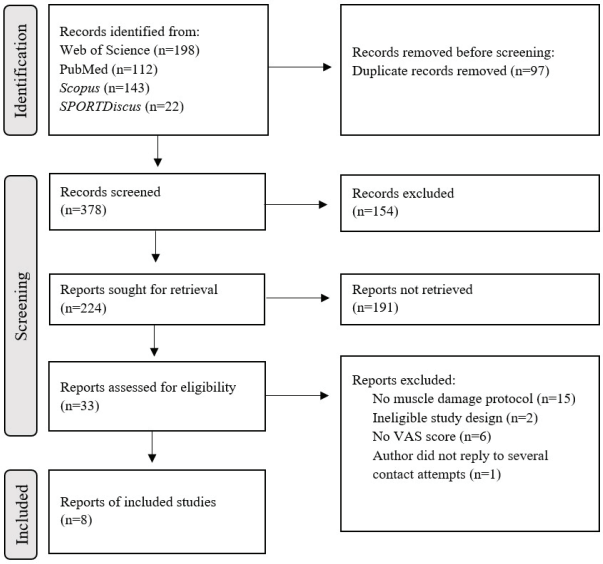

Figure 1. Flow diagram of literature search.

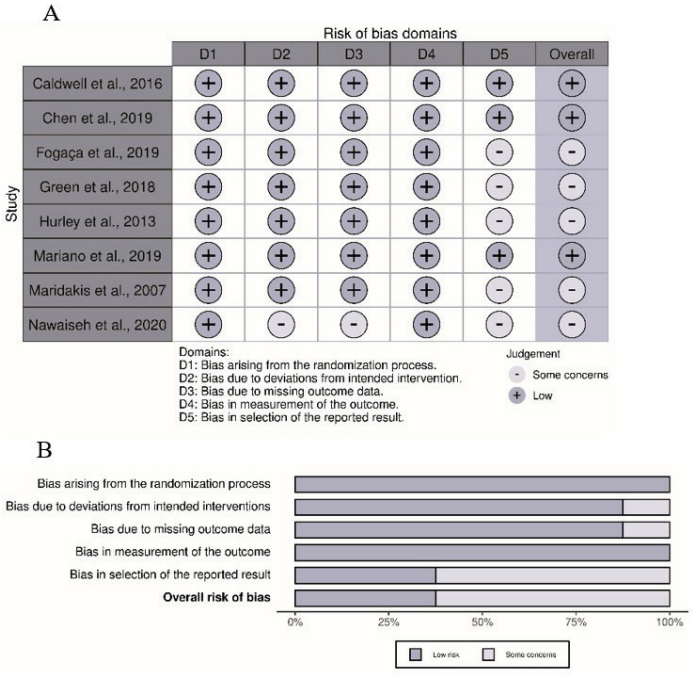

Figure 2. Risk of bias assessment of the included studies: (A) risk of bias summary; (B) risk of bias graph.

Statistical Methods

The Comprehensive Meta-Analysis free trial software (CMA- Version 2 Professional, Biostat Inc., Englewood, USA) was used to conduct all statistical analyses. In the analysis of continuous variables, the standardized mean difference (SMD) and the 95% confidence interval (CI) were computed. Heterogeneity was evaluated using the Chi-square test and the I^2 test. The fixed effects model was used if statistical heterogeneity was not observed ($p>0.05$ and I^2 <50%), while the random effects model was utilized when statistical heterogeneity was identified ($p<0.05$ and $I^2 \geq 50\%$).

Results

General Characteristics of the Included Studies

Out of the 378 initially identified studies, a total of eight randomized controlled trials were incorporated into this meta-analysis. Six of the studies had a crossover design, while two studies used a parallel design. Five trials were conducted in the USA (Al-Nawaiseh et al., 2022; Caldwell et al., 2017; Green et al., 2018; Hurley et al., 2013; Maridakis et al., 2007), 2 in Brazil (Fogaça et al., 2020; Santos-Mariano et al., 2019), and 1 in Taiwan (Chen et al., 2019). All studies were written in English. The subjects consisted of 81 males (70%) and 34 females (30%). Participant ages ranged from 18 to 52 years, with body mass indexes between 20.9 and 27.9. Three studies (Fogaça et al., 2020; Green et al., 2018; Hurley et al., 2013) administered caffeine before muscle damage, while 5 studies (Al-Nawaiseh et al., 2022; Caldwell et al., 2017; Chen et al., 2019; Maridakis et al., 2007; Santos-Mariano et al., 2019) administered caffeine after muscle damage. Caffeine doses varied among studies, with 1 study (Caldwell et al., 2017) using 3 mg/kg, 4 studies (Al-Nawaiseh et al., 2022; Hurley et al., 2013; Maridakis et al., 2007; Santos-Mariano et al., 2019) using 5 mg/kg, and 3 studies (Caldwell et al., 2017; Chen et al., 2019; Green et al.,

Table 1. Characteristics of the included studies

Reference (year)	Subjects info (Training status, sample size, gender, (mean ± SD age)	Study design	Method inducing DOMS	Caffeine dosage (mg. kg−1)	Timing of caffeine ingestion	Soreness data time point	Results
Maridakis et al. (2007)	College-aged 9 females (21,3±1,6)	Double-blind, crossover	Electrically stimulated eccentric exercise of the quadriceps	5 (capsules)	24 and 48 hours following EIMD	24 and 48 hours following EIMD	Caffeine could produce a large reduction in pain resulting
Hurley et al. (2013)	Resistance-trained athletes, 9 males (20±1)	Double-blind, crossover	Four sets of 10 biceps curls followed by a fifth set in which subjects completed as many repetitions as possible	5 (capsules)	60 minutes before completing 4 sets of 10 biceps curls	Before exercise, and 24, 48, 72, 96, and 120 hours after exercise	A significant difference on palpation values with caffeine ingestion on day 2
Caldwell et al. (2016)	Cyclist, 25 Male (53±10 years) 5 female (46±11 years)	Double-blind placebo-controlled	Endurance cycle ride (164-kilometer)	3 (caffeine pills)	Immediately after the ride and next 4 mornings and 3 afternoons	24, 48, and 72 hours following bicycle ride	The caffeine group tended to have lower overall ratings of perceived soreness
Green et al. (2018)	Physically active individuals, 8 male, 8 female, (24,3±4,3)	Double-blind, crossover	Ten sets of 10 eccentric isotonic quadriceps contractions of 3-second duration each on a seated leg extension machine	6 (capsules)	30 minutes before eccentric quadriceps contractions	Immediately before, immediately after, and 24 hours after EIMD	Caffeine or placebo treatments possessed no differences
Chen et al. (2019)	Elite college athletes,10 male (21,1±2,1), 10 female (20,4±1,2)	Double-blind randomized	30-minutes downhill running at a declination of 15% and 70% VO_{2max}	6 (capsules)	24 and 48 hours following EIMD	24, and 48 hours following EIMD	Acute caffeine supplementation is able to attenuate DOMS
Fogaça et al. (2019)	CrossFit athletes, 9 male (28±2)	Double-blind, crossover	CrossFit workout	6 (capsules)	60 minutes before a CrossFit workout	pre, post and 24 hours after the workout	Acute caffeine supplementation of was not able to alter DOMS
Mariano et al. (2019)	Jumper and sprinter athletes, 11 male (18,7±2,7)	Double-blind, crossover	A half-squat exercise (4 x 12 repetitions at 70% of 1 *Repetition Maximum*)	5 (capsules)	24, 48, and 72 hours after	24, 48, and 72 hours after EIMD	Caffeine had no influence on DOMS
Nawaiseh et al. (2020)	Runners, 9 male, 2 female, (24,5±6,3)	Double-blind, crossover	30-minutes downhill run on a treadmill set at -10% grade (70% VO_{2max})	5 (capsules)	60 minutes before the 5 km running	Immediately, 24, and 48 hours, following downhill running	Caffeine is not effective at reducing muscle soreness

DOMS= Delayed onset muscle soreness; EIMD= Exercise-induced muscle damage; SD= Standard deviation; $mg.kg^{-1}$= milligram/kilogram^{-1}

2018) using 6 mg/kg. Four studies (Green et al., 2018; Hurley et al., 2013; Maridakis et al., 2007; Santos-Mariano et al., 2019) induced muscle damage through eccentric exercise, while the other 4 studies (Al-Nawaiseh et al., 2022; Caldwell et al., 2017; Chen et al., 2019; Fogaça et al., 2020) used aerobic exercise (Table 1).

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Risk of Bias

All selected studies demonstrated a low risk of bias during the randomization process and reporting of outcome measurements. One study (Al-Nawaiseh et al., 2022) raised concerns about deviations from intended interventions and the presence of missing outcome data. Five studies (Al-Nawaiseh et al., 2022; Fogaça et al., 2020; Green et al., 2018; Hurley et al., 2013; Maridakis et al., 2007) presented some concerns regarding the selection of reported results (Figure 2).

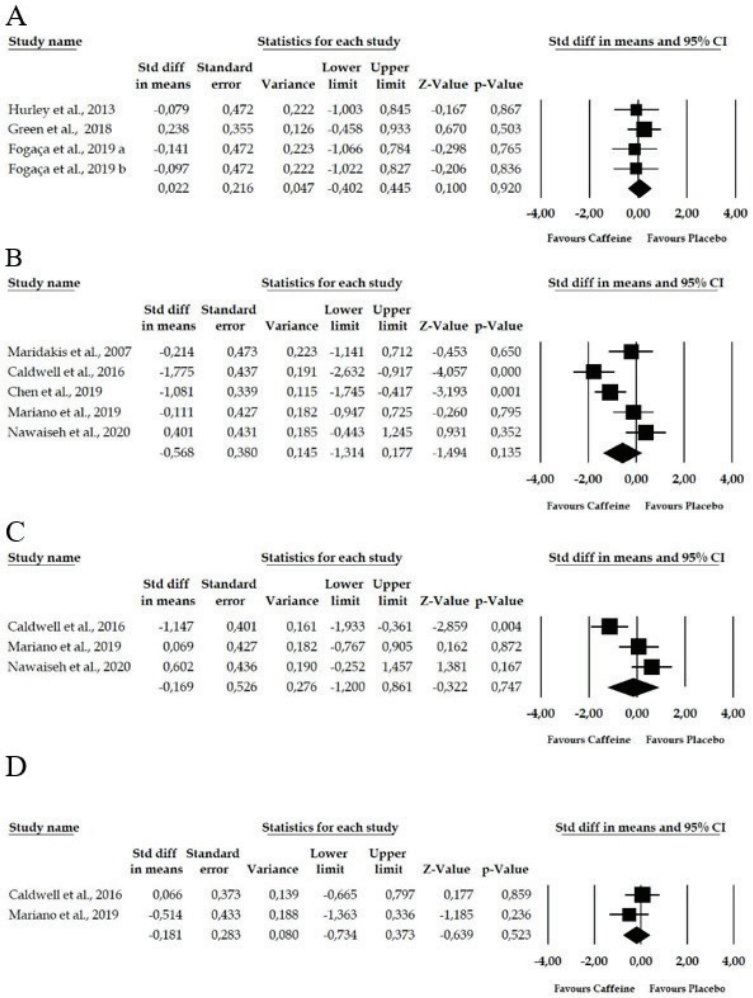

Figure 3. Forest plot for comparison of VAS at 24, 48 and 72 hours between caffeine supplementation and placebo: (A) VAS at 24 hour post-damage in caffeine ingestion before damage (a.biceps femoris muscle pain score, b. quadriceps femoris muscle pain score); VAS at (B) 24, (C) 48, and (D) 72 hours post-damage after caffeine ingestion.

Caffeine Effect on VAS at 24 hours after pre-damage caffeine intake

Effects of caffeine ingestion before muscle damage on DOMS-related pain after 24 hours later were evaluated by 3 studies (Fogaça et al., 2020; Green et al., 2018; Hurley et al., 2013). As Fogoça et al.(Fogaça et al., 2020) evaluated the pain score of the quadriceps and biceps femoris muscles individually, and the scores of both muscle groups were included in the analysis as separate values. No significant differences were found in the mean VAS scores for muscle soreness between the caffeine and placebo groups at 24 hours following exercise. (SMD=0,22, 95% CI -0,40, 0,44; p=0.920) (Figure 3-A). The analysis revealed a low level of heterogeneity across the studies. (Cochran's Q: 0,598, df (Q):3, p=0,897; I^2:0%).

Caffeine Effect on VAS at 24 hours after post-damage caffeine intake

Five studies examined the impact of caffeine consumption on pain associated with DOMS at 24 hours following muscle damage (Al-Nawaiseh et al., 2022; Caldwell et al., 2017; Chen et al., 2019; Maridakis et al., 2007; Santos-Mariano et al., 2019). Caldwell et al. (Caldwell et al., 2017) administered caffeine immediately after damage and at 24 hours, while other studies administered caffeine at 24 hours (Al-Nawaiseh et al., 2022; Chen et al., 2019; Maridakis et al., 2007; Santos-Mariano et al., 2019). No significant difference was found in pain scores between the caffeine group and the placebo group. The analysis revealed no significant difference between the caffeine and placebo groups in terms of pain scores (SMD=-0,568, 95% CI -1,31, 0,17; p=0.135) (Figure 3-B). Statistical heterogeneity was detected between the studies (Cochran's Q:16,596, df (Q):4, p=0,002; I^2:75,89%). Upon performing a subgroup analysis to determine the source of heterogeneity, the results suggested that the caffeine dose and study design could explain the heterogeneity, while exercise type (aerobic or resistance) could not.

Caffeine Effect on VAS at 48 hours after post-damage caffeine intake

The impact of caffeine consumption on VAS score 48 hours after muscle damage was investigated by three studies (Al-Nawaiseh et al., 2022; Caldwell et al., 2017; Santos-Mariano et al., 2019). There was no statistically significant difference between caffeine and plasebo consumption on pain score at 48 hours after muscle damage (SMD=-0.169, 95% CI -1,20, 0,86; p=0,747) (Figure 3-C). A high heterogeneity was seen across studies (Cochran's Q:9,353, df (Q):2, p=0,009; I^2:78,61%) (p=0,009, I^2=78,61).

Caffeine Effect on VAS at 72 hours after post-damage caffeine intake

Two studies investigated the impact of caffeine consumption on pain 72 hours following muscle damage. No improvement in VAS scores was identified after the ingestion of caffeine (SMD=-0,181, 95% CI -0,73, 0,37; p=0,523) (Figure 3-D). A low level of heterogeneity was observed between the studies (Cochran's Q:1,029, df (Q):1, p=0,310; I^2:2,78%).

Subgroup Analysis

A subgroup analysis was carried out to determine if there was evidence for the impact of different caffeine doses on pain scores following exercise-induced muscle damage. A subgroup analysis of (Al-Nawaiseh et al., 2022; Chen et al., 2019; Maridakis et al., 2007; Santos-Mariano et al., 2019) three studies evaluating the effect of 5-6 mg/kg caffeine dose on muscle damage was performed (SMD=-0,287, 95% CI -0,95, 0.37; p=0,398) and it was observed that 5-6 mg/kg caffeine had no significant effect on the pain score compared to placebo (Figure 4-A1). In the analysis of a study (Caldwell et al., 2017) evaluating the effect of 3 mg/kg caffeine (SMD=-1,775, 95% CI -2,63, 0,97; p<0,00) (Figure 4-A2), a substantial effect of 3 mg/kg caffeine on pain score was found compared to placebo.

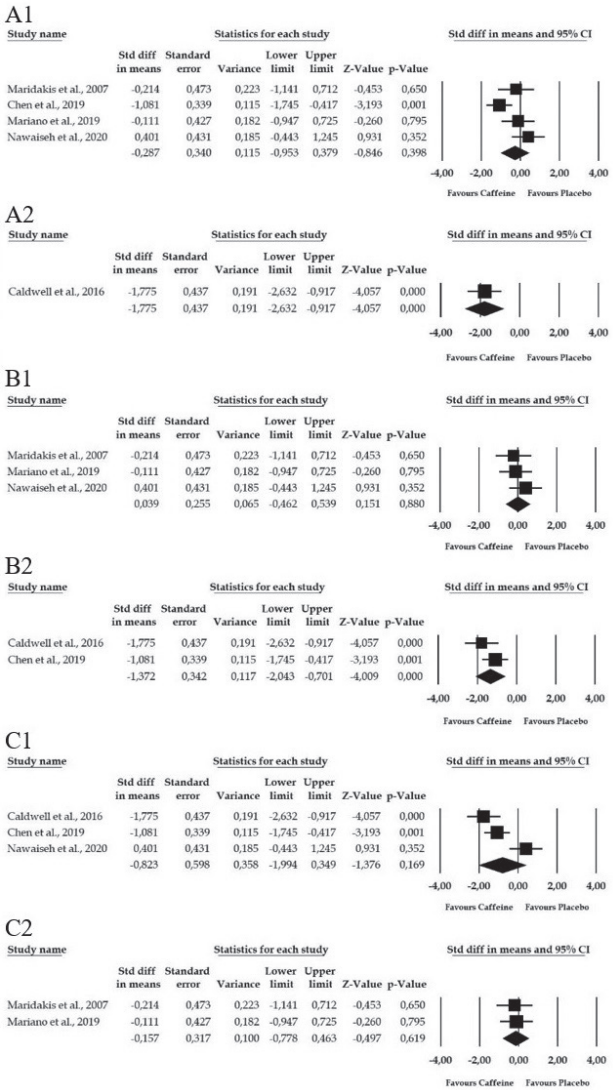

Figure 4. Subgroup analysis of VAS at 24 hours in groups ingested caffeine and placebo after muscle damage: (A1) 5-6 mg/kg caffeine; (A2) 3 mg/kg caffeine; (B1) crossover design; (B2) parallel design; (C1) aerobic exercise; (C2) resistance exercise.

A subgroup analysis of five studies was performed to examine the relationship between study design (crossover-parallel) and pain score during caffeine ingestion. For three crossover studies (Al-Nawaiseh et al., 2022; Maridakis et al., 2007; Santos-Mariano et al., 2019) compared to placebo, caffeine did not have a significant effect on pain (SMD=0,039, 95%

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CI -0,46, 0,53; p=0,880) (Figure 4-B1). In the analysis of two studies (Caldwell et al., 2017; Chen et al., 2019) evaluating the effect of caffeine with a parallel design (SMD=-1,372, 95% CI -2,04, -0,70; p<0,00) (Figure 4-B2), a significant effect of caffeine on pain score was observed compared to placebo.

Three studies (Al-Nawaiseh et al., 2022; Caldwell et al., 2017; Chen et al., 2019) were included in the subgroup analysis for the effect of caffeine use 24 hours after aerobic exercise-related muscle damage. The combined SMD of VAS score for the subgroup of patients with DOMS was -0,823 (95% CI -1,99, 0,34; p=0,169), indicated no significant decrease in VAS score in the caffeine consomption grup (Figure 4-C1). Two studies (Maridakis et al., 2007; Santos-Mariano et al., 2019) evaluating VAS scores of caffeine use 24 hours after resistance exercise-induced muscle damage were included in the subgroup analysis. Compared with placebo, the caffeine group did not show any significant improvement in pain (SMD=-0,157, 95% CI -0,77, 0,46; p=0,619) (Figure 4-C2).

Discussion

This meta-analysis investigated the influence of caffeine supplementation on pain caused by exercise-induced muscle damage. The results of this study show that caffeine supplementation, administered either before or after muscle damage, did not significantly influence the DOMS pain score compared to the control groups.

Caffeine is the most used ergogenic supplement among athletes, with a 75% usage rate before and during the competition (Del Coso et al., 2011). Caffeine increases cellular ion release by stimulating adrenaline secretion (Graham, 2001; Sökmen et al., 2008). When used after exercise, it increases the rate of new glycogen synthesis and glycogen accumulation (Pedersen et al., 2008). In addition, the elevation in heart rate and blood pressure, as well as the extension of the QTc interval resulting from caffeine intake after exercise suggest that the sympathetic recovery period is prolonged. It is important because it can disrupt the stability of autonomic function, especially after exercise termination (Bunsawat et al., 2015). It seems that caffeine use before or after muscle damage has quite different effects on muscle metabolism.

Because of various effects of caffeine on muscle metabolism, pre-exercise ingestion may influence damage formation, while post-exercise use may impact muscle recovery. In the pioneering study by Muljadi et al. (2021) the analysis included studies that assessed the effects of caffeine use on pain before, after, or both before and after exercise-induced damage. Unlike this study, in order to more clearly evaluate the effect of pre- or post-exercise caffeine use on pain, pre- or post-exercise caffeine ingestion was analyzed separately in this study. When the risk of bias assessment was made in the included RCTs, low bias was observed in 3 studies, while some concerns were observed in 5 studies.

First, randomize controlled studies evaluating caffeine use before exercise damage were analyzed to see the effect of pre-injury use on pain. Of the three studies in the literature examining the effect of caffeine use on DOMS-induced pain compared to placebo before muscle damage, Hurley et al. (2013) showed that caffeine was more effective, while Green et al. (2018) and Fogaça et al. (2020) found no difference at 24 hours later. Hurley et al. (2013) indicated that using caffeine in the days following intense resistance training could alleviate pain and facilitate an increase in the frequency of training sessions over time. In contrast, Green et al. (2018) and Fogaça et al. (2020) found that pre-injury caffeine use did not cause a significant reduction in perceived pain at 24 hours compared to placebo. In Muljadi et al. (2021) meta-analysis study, when 7 studies that evaluating the effect of caffeine before, after, or both before and after muscle damage were analyzed together, no significant difference was found in the change in pain score compared to placebo. Similarly, in this meta-analysis study, it was observed that consuming 5-6 mg/kg of caffeine only prior to the muscle damage did not have a significant impact on pain 24 hours later.

Although caffeine use increases the firing rate of muscles by increasing the release of dopamine and glutamate (Kalmar, 2005), according to the available data of this study, the consumption of 5-6 mg/kg of caffeine prior to muscle damage does not influence muscle pain. In order to reveal the effects of caffeine before muscle damage more clearly, studies involving more participants and evaluating different doses are required.

It has been stated that when caffeine is used after exercise, an increase in muscle glucose level is observed (Bunsawat et al., 2015), while it may also prolonged sympathetic recovery time (Pedersen et al., 2008). Five studies exist within the literature just looking at the effects of caffeine and placebo use on DOMS pain after exercise damage. While Chen (2019) and Caldwell (2017) report a more significant decrease in pain scores than placebo with caffeine ingestion, other studies did not find any advantage of caffeine over placebo. Of these studies, only Caldwell et al. (2017) used caffeine (3 mg/kg) both 4 days after the damage and immediately after muscle damage and reported a positive effect of caffeine on pain Analysis of the results from these studies revealed that caffeine consumption does not have a significant effect on exercise-related muscle pain at 24, 48, and 72 hours following muscle damage. When Muljadi et al. (2021) analyzed studies involving caffeine use before, after, or both before and after exercise, they demonstrated that caffeine was ineffective in alleviating DOMS pain at 24 and 72 hours, similar to this study. Differently, they found that caffeine supplements were effective in reducing DOMS pain 48 hours after exercise (Muljadi et al., 2021). In addition, Muljadi et al.'s (2021) meta-analysis study showed that caffeine use during exercise had no effect on Creatine kinase (CK) values are an indicator of muscle damage. Most of the studies examined in the analysis applied caffeine doses of 5-6 mg/kg. The hypoalgesic effects of caffeine may become evident after more rigorous exercise or with varying dosages. Spriet (2014) stated that low and very low doses of caffeine taken at the end of long-term exercise had an ergogenic effect in athletes and may be associated with lower side effects. Considering the studies of Caldwell et al.(2017) and Spriet (2014) together, low-dose caffeine use immediately after muscle damage and in the following days may have an affect on DOMS pain and perhaps muscle damage. Using a low dose of caffeine, such as 3 mg/kg, may help maintain muscle glucose levels without negatively impacting the sympathetic recovery process. To confirm this prediction, studies examining the effects of caffeine immediately following muscle damage and in the subsequent days are needed.

To identify the source of heterogeneity, subgroup analyses were performed with a focus on the 24-hour VAS as the primary outcome. Subgroup analysis was not conducted for the 48-hour mark due to insufficient studies for inclusion. In conclusion, while caffeine dose and study design could explain

the heterogeneity, exercise type (aerobic or resistance) could not account for it.

In the subgroup analysis, 5-6 mg/kg caffeine dose had no effect on DOMS pain, while 3mg/kg caffeine reduced the pain score. However, there is only one study using 3mg/kg caffeine, so it is not possible to clearly demonstrate the effect of low dose caffeine. In the literature, various doses of caffeine (5, 6, and 10 mg/kg) are employed in studies investigating its impact on muscle pain caused by exercise (Al-Nawaiseh et al., 2022; Chen et al., 2019; Maridakis et al., 2007; Motl et al., 2006; Santos-Mariano et al., 2019). Low-dose caffeine use (3 mg/kg) has also been reported to reduce muscle pain (Caldwell et al., 2017; Ganio et al., 2011). According to Spriet (2014) , low-dose caffeine use in athletes may have an ergogenic effect and is also associated with fewer side effects. Although this view of Spriet's (2014) supports the Caldwell study (2017), which used 3 mg/kg caffeine in its study, but more studies examining these effects of low-dose caffeine are needed.

The subgroup analysis according to study design revealed no significant difference in VAS scores between caffeine and placebo in crossover studies. In contrast, parallel studies found that caffeine had a significant effect on VAS scores compared to placebo. Consistent with the present study, Muljadi et al. (2021) observed a significant impact of caffeine on VAS scores in parallel-design studies, while crossover-design randomized controlled studies showed no significant effect. They also stated that crossover studies may not be very appropriate, because of the exercise damage to the muscle may last for a long time and may affect the formation of exercise damage again (Muljadi et al., 2021). Additionally, complete blinding can be difficult when using supplements and placebo in crossover studies, and the washout time of caffeine can cause problems.

The subgroup analysis assessing aerobic and resistance exercises indicated that the pain scores of the two groups were not statistically significantly different. In contrast, Muljadi et al. (2021) reported that caffeine intake 24 hours after resistance exercise reduced VAS. However, unlike in this analysis, they analyzed studies that used caffeine before or after exercise together. Due to the few studies available and the diversity in doses and exercise damage models, evaluating the analyses becomes challenging. Additional studies are required to explore the connection between caffeine and DOMS.

This is the first study to examine the impact of caffeine use on pain scores before or after DOMS using randomized controlled trials. Additionally, this study presents some limitations. The initial limitation is the relatively low number of studies included, reflecting the limited scope of available literature. As most studies included in the meta-analysis lacked reports of these values, there was not enough data to assess the muscle damage markers. Moderate to significant heterogeneity existed for several outcomes. The heterogeneity was attributed to the limited number of studies as well as the presence of studies with different exercise models and athlete groups. When assessing heterogeneity, most of the subgroup analyzes had to be conducted on a small number of studies. In addition, this meta-analysis included only English-language articles, and no registration was performed.

Conclusion

According to the current meta-analysis, a caffeine dosage of 5-6 mg/kg administered before or after muscle damage does not effectively reduce muscle pain associated with DOMS. It is possible that caffeine could have a hypoalgesic effect following a more strenuous exercise session or when administered at doses different from 5-6 mg/kg. Future studies may consider evaluating the effects of a 3 mg/kg caffeine dose on DOMS pain and potential side effects. Furthermore, to more clearly understand caffeine's analgesic effect, research evaluating various doses and timing of caffeine intake before and after exercise-induced damage is required.

Conflict of interest

The authors declare that there is no conflict of interest.

References

Al-Nawaiseh, A. M., Pritchett, R. C., Pritchett, K. K., Bataineh, M. F., Taifour, A. M., Bellar, D., Schoeff, M. A., Fox, B., Judge, A., & Judge, L. W. (2022). No significant effect of caffeine on five kilometer running performance after muscle damage. *International Journal for Vitamin and Nutrition Research. Internationale Zeitschrift Fur Vitamin- Und Ernahrungsforschung. Journal International De Vitaminologie Et De Nutrition*, *92*(5–6), 357–365. https://doi.org/10.1024/0300-9831/a000683

Bunsawat, K., White, D. W., Kappus, R. M., & Baynard, T. (2015). Caffeine delays autonomic recovery following acute exercise. *European Journal of Preventive Cardiology*, *22*(11), 1473–1479. https://doi.org/10.1177/2047487314554867

Caldwell, A. R., Tucker, M. A., Butts, C. L., McDermott, B. P., Vingren, J. L., Kunces, L. J., Lee, E. C., Munoz, C. X., Williamson, K. H., Armstrong, L. E., & Ganio, M. S. (2017). Effect of Caffeine on Perceived Soreness and Functionality Following an Endurance Cycling Event. *Journal of Strength and Conditioning Research*, *31*(3), 638–643. https://doi.org/10.1519/JSC.0000000000001608

Chen, H.-Y., Chen, Y.-C., Tung, K., Chao, H.-H., & Wang, H.-S. (2019). Effects of caffeine and sex on muscle performance and delayed-onset muscle soreness after exercise-induced muscle damage: A double-blind randomized trial. *Journal of Applied Physiology (Bethesda, Md.: 1985)*, *127*(3), 798–805. https://doi.org/10.1152/japplphysiol.01108.2018

Cheung, K., Hume, P., & Maxwell, L. (2003). Delayed onset muscle soreness: Treatment strategies and performance factors. *Sports Medicine (Auckland, N.Z.)*, *33*(2), 145–164. https://doi.org/10.2165/00007256-200333020-00005

Clarkson, P. M., & Sayers, S. P. (1999). Etiology of exercise-induced muscle damage. *Canadian Journal of Applied Physiology = Revue Canadienne De Physiologie Appliquee*, *24*(3), 234–248. https://doi.org/10.1139/h99-020

Del Coso, J., Muñoz, G., & Muñoz-Guerra, J. (2011). Prevalence of caffeine use in elite athletes following its removal from the World Anti-Doping Agency list of banned substances. *Applied Physiology, Nutrition, and Metabolism = Physiologie Appliquee, Nutrition Et Metabolisme*, *36*(4), 555–561. https://doi.org/10.1139/h11-052

Derry, C. J., Derry, S., & Moore, R. A. (2014). Caffeine as an analgesic adjuvant for acute pain in adults. *The Cochrane Database of Systematic Reviews*, *2014*(12), CD009281. https://doi.org/10.1002/14651858.CD009281.pub3

Doherty, M., Smith, P., Hughes, M., & Davison, R. (2004). Caffeine lowers perceptual response and increases power output during high-intensity cycling. *Journal of Sports Sciences*, *22*(7), 637–643. https://doi.org/10.1080/02640410310001655741

 DOI 10.26773/mjssm.250306

Drevon, D., Fursa, S. R., & Malcolm, A. L. (2017). Intercoder Reliability and Validity of WebPlotDigitizer in Extracting Graphed Data. *Behavior Modification*, *41*(2), 323–339. https://doi.org/10.1177/0145445516673998

Fogaça, L. J., Santos, S. L., Soares, R. C., Gentil, P., Naves, J. P., Dos Santos, W. D., Pimentel, G. D., Bottaro, M., & Mota, J. F. (2020). Effect of caffeine supplementation on exercise performance, power, markers of muscle damage, and perceived exertion in trained CrossFit men: A randomized, double-blind, placebo-controlled crossover trial. *The Journal of Sports Medicine and Physical Fitness*, *60*(2), 181–188. https://doi.org/10.23736/S0022-4707.19.10043-6

Ganio, M. S., Johnson, E. C., Lopez, R. M., Stearns, R. L., Emmanuel, H., Anderson, J. M., Casa, D. J., Maresh, C. M., Volek, J. S., & Armstrong, L. E. (2011). Caffeine lowers muscle pain during exercise in hot but not cool environments. *Physiology & Behavior*, *102*(3–4), 429–435. https://doi.org/10.1016/j.physbeh.2010.12.005

Graham, T. E. (2001). Caffeine and exercise: Metabolism, endurance and performance. *Sports Medicine (Auckland, N.Z.)*, *31*(11), 785–807. https://doi.org/10.2165/00007256-200131110-00002

Green, M. S., Martin, T. D., & Corona, B. T. (2018). Effect of Caffeine Supplementation on Quadriceps Performance After Eccentric Exercise. *Journal of Strength and Conditioning Research*, *32*(10), 2863–2871. https://doi.org/10.1519/JSC.0000000000002530

Hübscher, M., Vogt, L., Bernhörster, M., Rosenhagen, A., & Banzer, W. (2008). Effects of acupuncture on symptoms and muscle function in delayed-onset muscle soreness. *Journal of Alternative and Complementary Medicine (New York, N.Y.)*, *14*(8), 1011–1016. https://doi.org/10.1089/acm.2008.0173

Hurley, C. F., Hatfield, D. L., & Riebe, D. A. (2013). The effect of caffeine ingestion on delayed onset muscle soreness. *Journal of Strength and Conditioning Research*, *27*(11), 3101–3109. https://doi.org/10.1519/JSC.0b013e3182a99477

Kalmar, J. M. (2005). The influence of caffeine on voluntary muscle activation. *Medicine and Science in Sports and Exercise*, *37*(12), 2113–2119. https://doi.org/10.1249/01.mss.0000178219.18086.9e

Lewis, P. B., Ruby, D., & Bush-Joseph, C. A. (2012). Muscle soreness and delayed-onset muscle soreness. *Clinics in Sports Medicine*, *31*(2), 255–262. https://doi.org/10.1016/j.csm.2011.09.009

Maridakis, V., O'Connor, P. J., Dudley, G. A., & McCully, K. K. (2007). Caffeine attenuates delayed-onset muscle pain and force loss following eccentric exercise. *The Journal of Pain*, *8*(3), 237–243. https://doi.org/10.1016/j.jpain.2006.08.006

Matsumura, M. D., Zavorsky, G. S., & Smoliga, J. M. (2015). The Effects of Pre-Exercise Ginger Supplementation on Muscle Damage and Delayed Onset Muscle Soreness. *Phytotherapy Research: PTR*, *29*(6), 887–893. https://doi.org/10.1002/ptr.5328

Motl, R. W., O'connor, P. J., Tubandt, L., Puetz, T., & Ely, M. R. (2006). Effect of caffeine on leg muscle pain during cycling exercise among females. *Medicine and Science in Sports and Exercise*, *38*(3), 598–604. https://doi.org/10.1249/01.mss.0000193558.70995.03

Muljadi, J. A., Kaewphongsri, P., Chaijenkij, K., & Kongtharvonskul, J. (2021). Effect of caffeine on delayed-onset muscle soreness: A meta-analysis of RCT. *Bulletin of the National Research Centre*, *45*(1), 197. https://doi.org/10.1186/s42269-021-00660-5

Pedersen, D. J., Lessard, S. J., Coffey, V. G., Churchley, E. G., Wootton, A. M., Ng, T., Watt, M. J., & Hawley, J. A. (2008). High rates of muscle glycogen resynthesis after exhaustive exercise when carbohydrate is coingested with caffeine. *Journal of Applied Physiology (Bethesda, Md.: 1985)*, *105*(1), 7–13. https://doi.org/10.1152/japplphysiol.01121.2007

Pollock, N., James, S. L. J., Lee, J. C., & Chakraverty, R. (2014). British athletics muscle injury classification: A new grading system. *British Journal of Sports Medicine*, *48*(18), 1347–1351. https://doi.org/10.1136/bjsports-2013-093302

Santos-Mariano, A. C., Tomazini, F., Felippe, L. C., Boari, D., Bertuzzi, R., De-Oliveira, F. R., & Lima-Silva, A. E. (2019). Effect of caffeine on neuromuscular function following eccentric-based exercise. *PloS One*, *14*(11), e0224794. https://doi.org/10.1371/journal.pone.0224794

Sawynok, J. (1998). Adenosine receptor activation and nociception. *European Journal of Pharmacology*, *347*(1), 1–11. https://doi.org/10.1016/s0014-2999(97)01605-1

Sökmen, B., Armstrong, L. E., Kraemer, W. J., Casa, D. J., Dias, J. C., Judelson, D. A., & Maresh, C. M. (2008). Caffeine use in sports: Considerations for the athlete. *Journal of Strength and Conditioning Research*, *22*(3), 978–986. https://doi.org/10.1519/jsc.0b013e3181660cec

Spriet, L. L. (2014). Exercise and sport performance with low doses of caffeine. *Sports Medicine (Auckland, N.Z.)*, *44 Suppl 2*(Suppl 2), S175-184. https://doi.org/10.1007/s40279-014-0257-8

Sterne, J. A. C., Savović, J., Page, M. J., Elbers, R. G., Blencowe, N. S., Boutron, I., Cates, C. J., Cheng, H.-Y., Corbett, M. S., Eldridge, S. M., Emberson, J. R., Hernán, M. A., Hopewell, S., Hróbjartsson, A., Junqueira, D. R., Jüni, P., Kirkham, J. J., Lasserson, T., Li, T., … Higgins, J. P. T. (2019). RoB 2: A revised tool for assessing risk of bias in randomised trials. *BMJ (Clinical Research Ed.)*, *366*, l4898. https://doi.org/10.1136/bmj.l4898

Tauler, P., Martinez, S., Martinez, P., Lozano, L., Moreno, C., & Aguiló, A. (2016). Effects of Caffeine Supplementation on Plasma and Blood Mononuclear Cell Interleukin-10 Levels After Exercise. *International Journal of Sport Nutrition and Exercise Metabolism*, *26*(1), 8–16. https://doi.org/10.1123/ijsnem.2015-0052

Tauler, P., Martínez, S., Moreno, C., Monjo, M., Martínez, P., & Aguiló, A. (2013). Effects of caffeine on the inflammatory response induced by a 15-km run competition. *Medicine and Science in Sports and Exercise*, *45*(7), 1269–1276. https://doi.org/10.1249/MSS.0b013e3182857c8a