

REVIEW

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Effect of caffeine on delayed-onset muscle soreness: a meta-analysis of RCT

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Abstract

Background: There are multiple strategies that have been suggested to attenuate delayed-onset muscle soreness (DOMS). Caffeine has been shown to assist with blocking pain associated with DOMS. However, currently there is still controversy over the effects of caffeine use.

Main body: We conducted a meta-analysis to compare pain associated with muscle soreness by both the VAS and indirect markers by CK of caffeine and placebo after exercise. The meta-analysis was carried out in accordance with the PRISMA guidelines. Relevant studies from Medline and Scopus published up to May 20, 2021, were included, which resulted in a total of 477 and 132 studies being retrieved from Scopus and Medline, respectively. Seven studies met the inclusion criteria, and in these, there were 68 persons in the caffeine group and 74 persons in the placebo group. A visual analog score of muscle soreness was recorded pre-exercise, immediately post-exercise, and at one to four days post-exercise; the scores at these time points in the caffeine group as compared to those in the placebo group progressed from 0.00 (95% CI -0.51, 0.50) to -0.20 (-1.09, 0.69), -0.92 (-2.20, 0.36), -1.02 (-1.86, -0.19), 0.00 (-0.36, 0.36), and 0.18 (-0.56, 0.92), respectively. No statistically significant differences were noted for CK between the two groups at 24 h post-exercise.

Short conclusion: Our meta-analysis results indicate that caffeine supplements reduce delayed-onset muscle soreness when compared to a placebo 48 h after exercise. However, at 24 h post-exercise, caffeine can reduce DOMS only in people who worked on resistant exercise. The CK used in this meta-analysis did not show any differences.

Trial registration: PROSPERO CRD42021260248.

Level of evidence: I.

Keywords: DOMS, Caffeine, Exercise-induced muscle soreness, Meta-analysis

Background

Delayed-onset muscle soreness (DOMS) normally occurs 1 to 2 days after unaccustomed activity and eccentric muscle contraction, with symptoms including muscle soreness and discomfort (Chen et al. 2019; Connolly et al. 2003). DOMS is normally a symptom of exercise-induced muscle damage (EIMD) (Howatson and Someren 2008). Even among well-trained athletes, high-intensity exercise

that involves unaccustomed or eccentric muscle contractions can lead to microscopic intramuscular tears and exaggerated inflammatory responses (Jobin et al. 1999; Shehzad et al. 2011; Jäger et al. 2019). An inflammatory response and the production of reactive oxygen species (ROS) are triggered by this mechanical stress. The reason for this process is that mechanical stress promotes the activation of transcription factors, such as nuclear factor- κ B (NF- κ B), which limits an athlete's performance and daily activities (Paulsen et al. 2012; García-López et al. 2007). EIMD can be manifested by prolonged decline in muscle strength, reduction in range of motion (ROM), swelling, DOMS, and an increase in blood

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muscle proteins and creatine kinase (CK) activity (Warren et al. 1999; Tanabe et al. 2015). Therefore, post-exercise muscle damage should be prevented or minimized.

Caffeine is a stimulant that is widely consumed and has been shown to exhibit many physiological and psychological effects (Astorino and Roberson 2010; Al-Nawaiseh et al. 2020). For many decades, caffeine supplements have been used legally as an ergogenic substance to enhance endurance and attenuate DOMS during exercise under EIMD (Burke 2008). Therefore, athletes use caffeine in order to improve their agility and performance (Astorino and Roberson 2010; Doherty and Smith 2004). The rationale of the increase in performance could be caused by the release of cortisol and beta-endorphins, leading to less exhaustion during physical activities (Costill et al. 1978; Doherty and Smith 2005; Graham 2001; Kalmar and Cafarelli 1999, 2004; Laurent et al. 2000; Tarnopolsky and Cupido 2000). Caffeine has been shown to attenuate DOMS and increase muscle strength and power (Grgic and Pickering 2019; Grgic et al. 2018; Warren et al. 2010) via an enhanced Ca^{2+} efflux from the sarcoplasmic reticulum (Lamb et al. 2001), a direct Ca^{2+} -sensitizing effect on skeletal muscle (Tallis et al. 2015), and an increase in $\text{Na}^+ - \text{K}^+ - \text{ATPase}$ activity resulting from decreased serum levels of K^+ (Sökmen et al. 2008). This attenuating effect of caffeine has been shown by clinical studies involving chronic headache, migraine, and postoperative pain (Chen et al. 2019; Sökmen et al. 2008). Although there are many reports of caffeine ingestion attenuating DOMS during exercise under EIMD, the effects of caffeine supplements remain unclear. Several studies reported that caffeine is able to reduce and attenuate delayed-onset muscle soreness (Caldwell et al. 2017; Nobahar 2013; Maridakis et al. 2007). However, others have reported that caffeine is unable to affect DOMS (Chen et al. 2019; Hurley et al. 2013; Al-Nawaiseh et al. 2020; Fogaça et al. 2020). No meta-analysis related to this topic has been published yet. To gain a better understanding of how caffeine supplements affect delayed-onset muscle soreness symptoms, we performed a meta-analysis based on the outcomes from studies in the literature.

Main text

Search strategy and data sources

This review was conducted according to the transparent reporting of systematic reviews and meta-analyses (PRISMA guideline 2009). The search was performed in the PubMed and Scopus databases, with studies up to May 20, 2021, considered. The following keywords were used as search terms: ((Caffeine) OR (coffee)) AND ((delayed onset muscle soreness) OR (DOMS) OR (Muscle soreness) OR (Muscle pain)). Reference lists of all

included studies were screened manually for further eligible articles. The studies were screened independently by two authors (J.M. and P.K.) against the eligibility criteria based on titles and abstracts using the bibliographical software package EndNote version X7. Disagreements were resolved regarding inclusion and exclusion criteria of a study with a third author (J.K.).

Selection criteria

Studies were included if they met the following criteria: (a) RCT and quasi-RCT studies; (b) reported outcomes based on the muscle soreness index (VAS) or creatine kinase (CK); (c) compared clinical outcomes between a caffeine supplement and placebo; and (d) had adequate data for extraction and pooling. We excluded studies if they used a combination of interventions besides caffeine supplements, and if they were experimental studies using animals, reviews, letters to the editor, or case reports and non-English languages studies.

Data extraction and methodology quality assessment

The data were extracted from each study through structured data extraction forms by two reviewers (J.M. and P.K.), using data extraction forms. The items extracted were baseline characteristics of the study including average age, sex, study design, mean follow-up time, and caffeine dosage. Clinical outcome data (number of subjects and mean and SD of VAS and CK) between groups were extracted, which was followed by data extraction of frequencies (adverse effects) between treatment groups. When any disagreements in opinion arose, a third author (J.K.) made the final decision. Quality assessment was performed by two authors (J.M. and K.C.) according to the Cochrane Collaboration tool for evaluating the risk of bias in order to avoid the distortion of the meta-analysis outcomes (Higgins et al. 2011). RCT studies were assessed by risk of bias following the PRISMA guideline recommendation (Liberati et al. 2009) based on sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other sources of bias. Any conflicts between reviewers related to quality assessment were settled by a third reviewer (J.K.).

Outcomes of interest

The outcomes considered were the VAS of muscle soreness and CK. The measurement of those outcomes was the same as reported in the original studies, namely VAS of muscle soreness (0–10), with lower values equivalent to better outcomes, and CK, with lower values equivalent to better outcomes.

Statistical methods

For continuous variables, data were pooled as an unstandardized mean difference (UMD) with 95% confidence intervals (CI). The heterogeneity across the studies was assessed using the Q statistic and I² statistic to quantify the degree of heterogeneity. An I² value of 0% was considered as no heterogeneity, 25% as low, 50% as moderate, and 75% as high heterogeneity. The statistical significance of heterogeneity was set with a P value of <0.10. A random-effect model was used if I²>25; otherwise, a fixed-effect model was applied. In order to explore the cause of heterogeneity, meta-regression was applied in the meta-regression model. According to the results of the meta-regression, sensitivity analyses were performed by leave-one-out to assess the robustness of a pooled conclusion. Funnel plots and an Egger test were used to assess publication bias (Egger et al. 1997; Palmer et al. 2018). The metatrim and fill method was used to estimate the number of studies that might be missing and to adjust the pooled estimate (Duval and Tweedie 2000).

Data were analyzed using STATA version 15.0 (Stata-Corp. 2017). A P value of <0.05 was considered statistically significant, while a P value of <0.10 was considered as a threshold of significant heterogeneity.

Results

A total of 477 AND 132 studies were retrieved from Scopus and Medline, respectively (Fig. 1). Of these, 70 duplicated studies and 532 non-relevant studies were excluded. The remaining seven studies met the inclusion criteria. The characteristics of the seven studies (Chen et al. 2019; Al-Nawaiseh et al. 2020; Caldwell et al. 2017; Nobahar 2013; Maridakis et al. 2007; Hurley et al. 2013; Fogaça et al. 2020) are summarized in Table 1. All studies were RCTs, three had a parallel design and four used a crossover design. Three studies involved resistance exercise, while four studies focused on aerobic exercises. All seven studies reported post-exercise muscle soreness using VAS. An indirect marker of muscle damage was reported using CK in four of the studies. The mean age

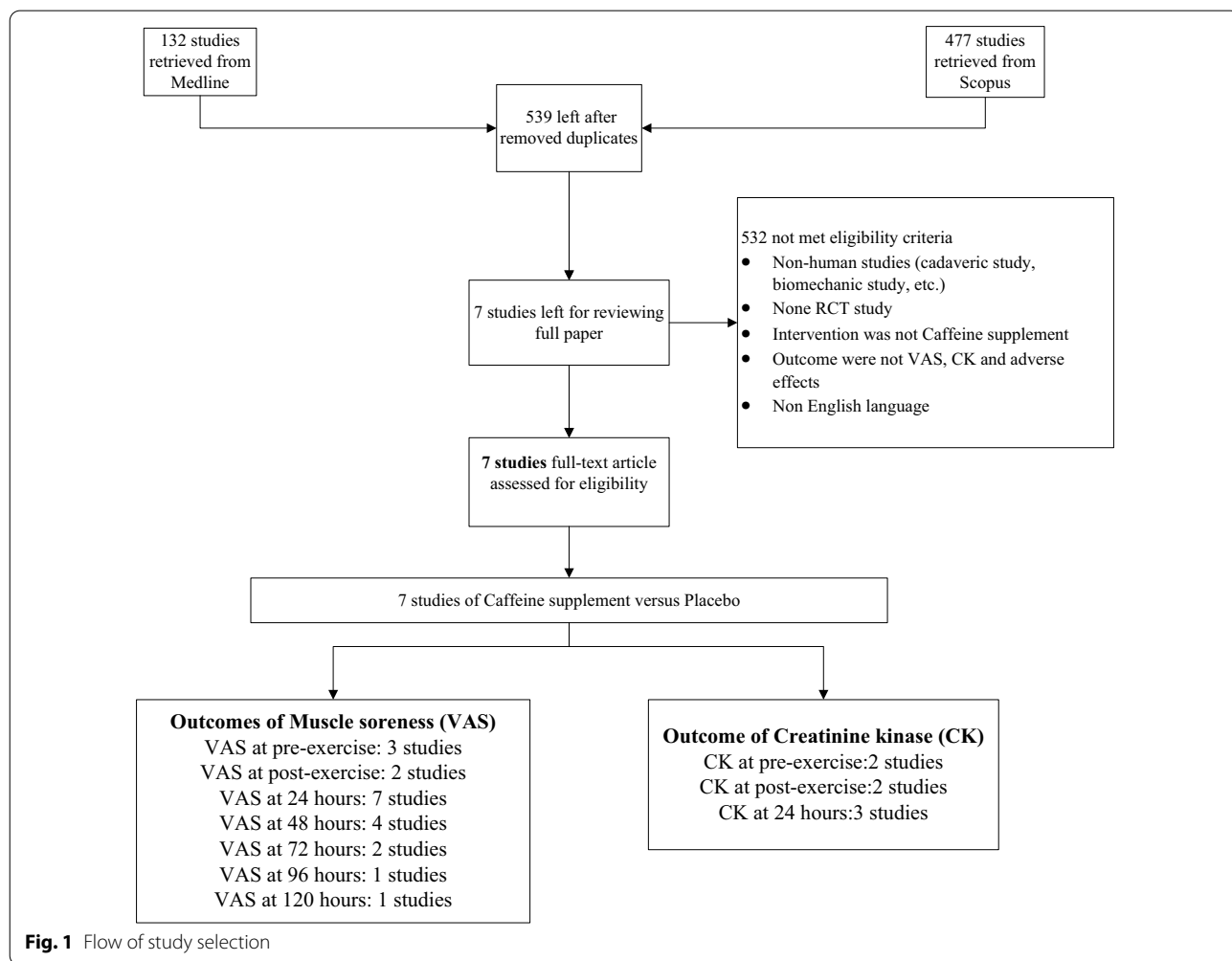


Fig. 1 Flow of study selection

Table 1 Characteristics of included studies

Author	Year	Country	N	Nc	Np	RCT	N (Male %)	Age (mean)	Outcome	Exercise	Dose (mg/kg)	BMI
Chen HY	2019	Taiwan	20	10	10	Parallel	50	20.75	CK VAS	Aerobic	6	21.75
Fogaca LJ	2020	Brazil	9	9	9	Crossover	100	28	CK VAS	Resistance	6	25.5
Hurley CF	2013	Rhode Island	9	9	9	Crossover	100	20	CK VAS	Resistance	5	-
Al-Nawaiseh AM	2020	USA	11	11	11	Crossover	81.8	24.5	VAS	Aerobic	5	23.18
Maridakis V	2007	Georgia	9	9	9	Crossover	0	21.3	VAS	Resistance	5	20.9
Nobahar M	2013	Iran	16	8	8	Parallel	0	22.5	CK VAS	Aerobic	1	-
Caldwell AR	2017	USA	30	12	18	Parallel	83.3	51.83	VAS	Aerobic	3	-

and body mass index (BMI) of participants ranged from 20 to 52 years and from 20.9 to 25.5, respectively. Two studies reported the proportion of male participants as 0%, while four studies were from 50 to 100% male. The caffeine dosages used were 1, 3, 5, and 6 mg/kg in 1, 1, 3, and 2 studies, respectively.

Risk of bias in included studies

All seven studies reported with selective and incomplete outcomes, while most used blinding (six out of the seven studies). All studies had unclear sequence generation data and had no allocation of concealment data (Table 2).

Outcomes

VAS of muscle soreness pre- and post-exercise at 24, 48, 72, and 96 h

The mean difference in VAS of muscle soreness between the caffeine and placebo test groups pre- and post-exercise at 24, 48, 72, and 96 h is shown in Table 3 and Fig. 2. The pooled UMDs of the caffeine group were -0.00 (95% CI -0.51, 0.50), -0.20 (-1.09, 0.69), -0.92 (-2.20, 0.36), -1.02 (-1.86, -0.19), -0.00 (-0.36, 0.36), and 0.18 (-0.56, 0.92) in comparison with those of the placebo group in the pre-exercise period and at 0, 24, 48, 72, and 96 h post-exercise, respectively. Thus, the mean VAS of muscle soreness differed significantly between

the two groups by a score of approximately 1 at 48 h and borderline significantly by 0.9 at 24 h (Table 3 and Fig. 2). There were no statistically significant differences between the two groups during the pre-exercise period, and post-exercise after 72 and 96 h. When separately fitting the mean age, gender, study design, mean follow up time, and dose of caffeine supplement at baseline in a meta-regression analysis, only the type of exercise (resistance or aerobic) was able to explain the heterogeneity. Subgroup analysis was performed for the three studies with resistance exercise, and comparing the caffeine and placebo groups showed no heterogeneity ($I^2=0\%$), while in the four studies that used aerobic exercise there was high heterogeneity between the caffeine and placebo groups ($I^2=99.5\%$) (Fig. 3). The mean VASs were -1.08 (95% CI -1.71, -0.45) and -0.89 (95% CI -2.59, 0.81). No evidence of publication bias was suggested by Egger's test and a contour funnel plot (bias = -2.53, $p=0.642$; bias = 4.86, $p=0.069$).

CK at pre- and post-exercise and 24 h later

The mean values of CK between the caffeine and placebo groups in the pre-exercise period and 0 and 24 h post-exercise are shown in Table 4 and Fig. 4. The pooled UMDs were 3.72 (95% CI -41.84, 49.28), 31.67 (29.50, 33.85), and 49.84 (-73.13, 172.82) U/L, i.e., the mean CK

Table 2 Risk of bias assessment

Author	Sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective outcome report
Chen HY	U	N	Y	Y	Y
Fogaca LJ	U	N	Y	Y	Y
Hurley CF	U	N	Y	Y	Y
Al-Nawaiseh AM	U	N	Y	Y	Y
Maridakis V	U	N	Y	Y	Y
Nobahar M	U	N	U	Y	Y
Caldwell AR	U	N	Y	Y	Y

Table 3 VAS

Author	Caffeine			Placebo		
	N	Mean	SD	N	Mean	SD
<i>A) VAS Pre-exercise</i>						
Lorruama J	9	4.7	3.67	9	4.9	3.37
Caitlin F	9	0.149	0.179	9	0.298	0.417
Maridakis V	9	2.66	1.56	9	1.82	1.08
UMD (95% CI)	− 0.00 (− 0.51, 0.50)					
<i>B) VAS Post-exercise</i>						
Al-Nawaiseh AM	11	3.927	2.235	11	4.009	1.956
Maridakis V	9	1.39	1.31	9	1.63	0.89
UMD (95% CI)	− 0.20 (− 1.09, 0.69)					
<i>C) VAS at 24 h</i>						
Chen HY	10	0.7525	0.1303	10	0.865	0.069
Lorruama J	9	5	3.38	9	5.5	3.08
Caitlin F	9	2.59	1.25	9	3.571	0.506
Al-Nawaiseh AM	11	5.506	1.64	11	5.022	1.38
Maridakis V	9	0.95	1.03	9	2.2	1.03
Nobahar M	8	2.5	0.175	8	5	0.175
Caldwell AR	12	1.45	2.45	18	2.78	1.67
UMD (95% CI)	− 0.92 (− 2.20, 0.36)					
<i>D) VAS at 48 h</i>						
Caitlin F	9	2.5	1.25	9	4.107	0.506
Al-Nawaiseh AM	11	5.3	2.204	11	3.973	2.207
Maridakis V	9	0.56	1.02	9	1.81	1.01
Caldwell AR	12	0.45	0.78	18	1.78	1.33
UMD (95% CI)	− 1.02 (− 1.86, − 0.19)					
<i>E) VAS at 72 h</i>						
Caitlin F	9	1.369	0.476	9	1.786	0.923
Caldwell AR	12	1	0.88	18	1.22	1.1
UMD (95% CI)	0.0 (− 0.36, 0.36)					
<i>F) VAS at 96 h</i>						
Caitlin F	9	0.952	0.774	9	0.774	0.833
UMD (95% CI)	0.18 (− 0.56, 0.96)					

difference was approximately 32 U/L, which was a statistically significant difference between the groups in the post-exercise period (Table 4 and Fig. 4). The heterogeneity could not be explained by any of the covariates. No evidence of publication bias was suggested by Egger’s test and a contour funnel plot (bias = 1.67, $p = 0.188$).

Analysis in RCT with parallel design

The UMDs of VAS muscle soreness between caffeine and placebo were − 1.31 (95% CI − 3.27, 0.65), − 1.33 (95% CI − 2.09, − 0.59), and − 0.22 (95% CI − 0.22: − 0.93, 0.49) at 24, 48, and 72 h post-exercise, respectively (Fig. 5). The mean VAS muscle soreness between the caffeine and placebo groups differed significantly by approximately 1.3 at 48 h post-exercise. The differences in the mean

values of CK between the caffeine and placebo groups at 0 and 24 h post-exercise were 31.7 (95% CI 29.49, 33.85) and − 15 (− 16.03, − 13.97) (Fig. 6). Thus, the mean CK of the caffeine group was statistically significant higher by approximately 32 U/L immediately post-exercise, while it was statistically significant lower by 15 U/L at 24 h post-exercise when compared with the placebo group.

Analysis in RCT with crossover design

The UMDs of VAS muscle soreness between caffeine and placebo were − 0.68 (95% CI − 1.47, 0.11), − 0.76 (95% CI − 2.08, 0.56), and − 0.42 (95% CI − 1.10, 0.26) at 24, 48, and 72 h post-exercise (Fig. 5). There were no significant differences in the mean VAS of muscle soreness between the two groups at 24, 48, and 72 h post-exercise. The

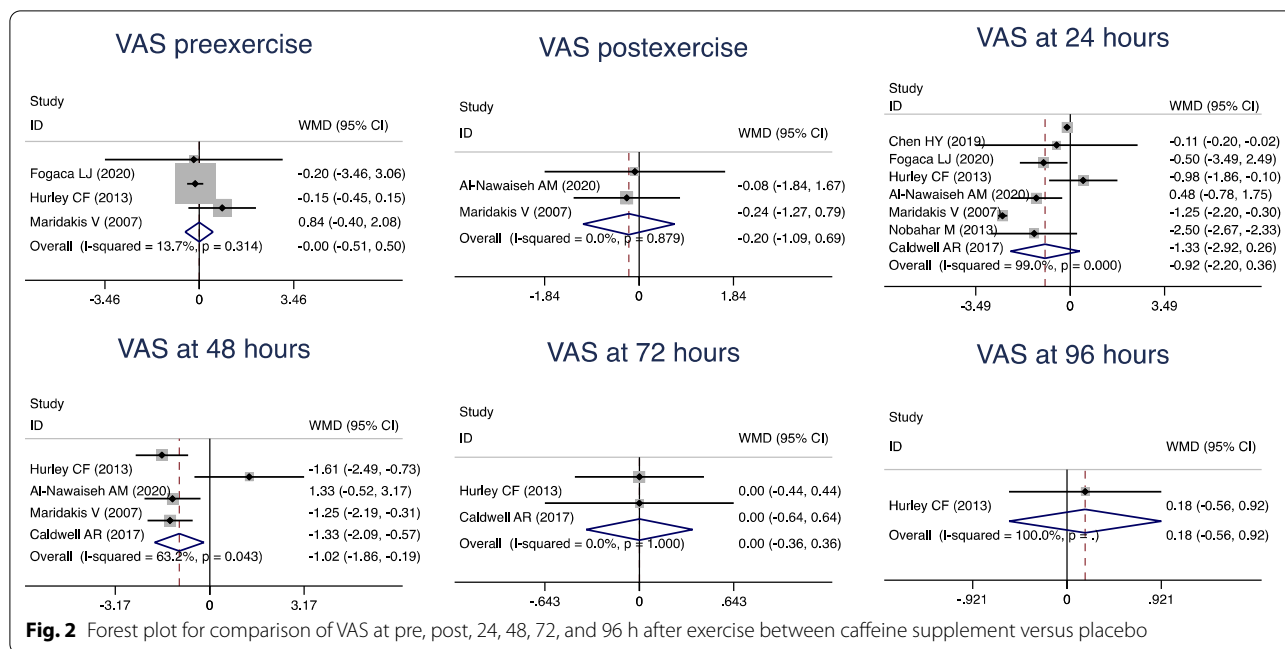


Fig. 2 Forest plot for comparison of VAS at pre, post, 24, 48, 72, and 96 h after exercise between caffeine supplement versus placebo

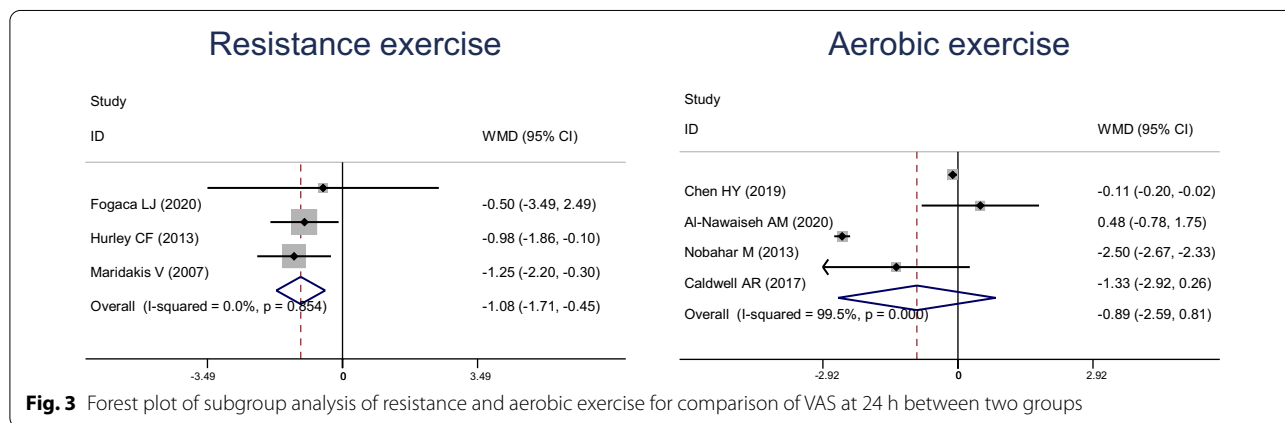


Fig. 3 Forest plot of subgroup analysis of resistance and aerobic exercise for comparison of VAS at 24 h between two groups

mean CK values for the caffeine and placebo groups at 0 and 24 h post-exercise were 71 (95% CI – 197.96, 333.96) and 170.87 (– 124.63, 466.37), respectively (Fig. 6), and this was not a statistically significant difference.

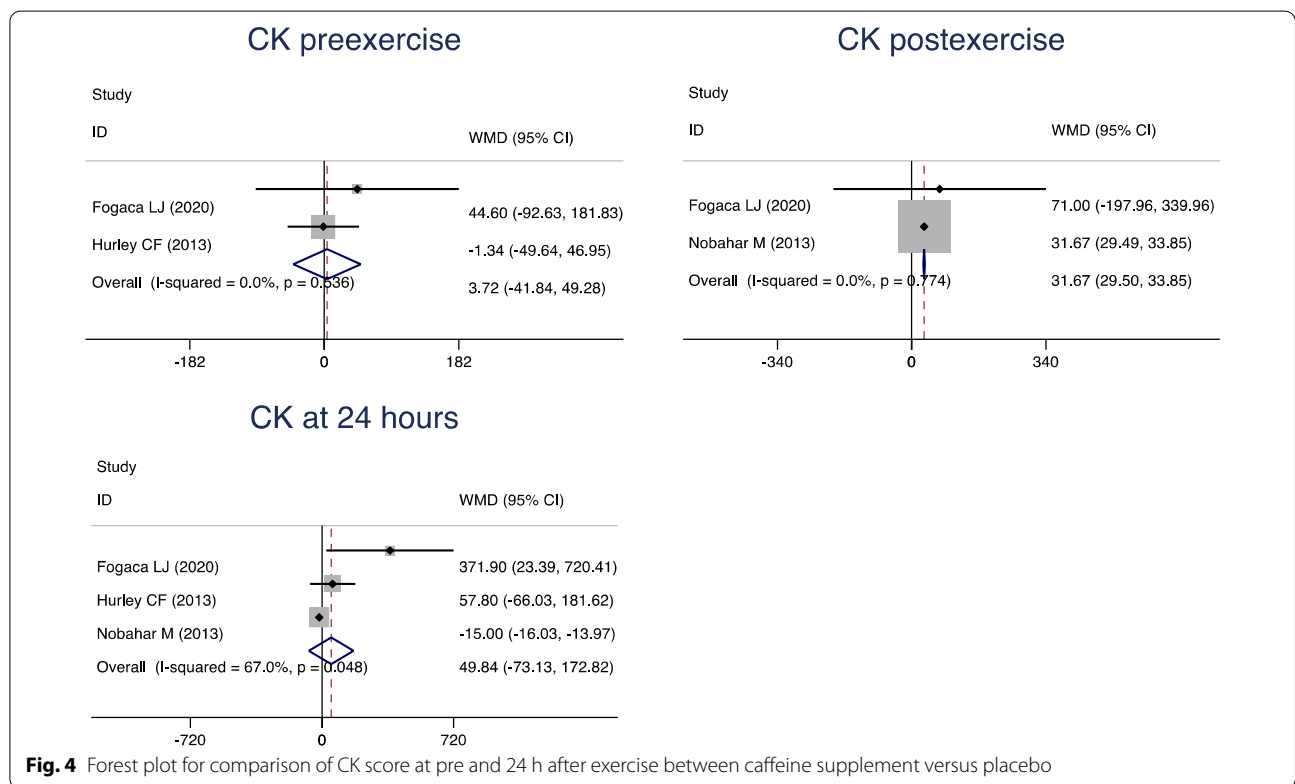
Discussion

This review indicated that people who took caffeine supplements before and/or after exercise had pain scores about 1 lower than those who took a placebo 48 h post-exercise. For indirect markers of muscle damage, the people who took caffeine supplements before and/or after exercise had higher CK scores by about 32 U/L than those who took a placebo. However, VASs exhibited no significant difference between the two groups at 24, 72, and 96 h. After performing a subgroup analysis including

the type of exercise and RCT design (parallel or crossover), the results showed that patients who had performed resistant exercises with caffeine supplements had significantly lower post-exercise pain VASs at 24 h than those in the placebo group. Caffeine supplements made no significant difference to VAS pain scores at 24 h post-exercise in patients who performed aerobic exercise when compared to those in the placebo group. When we used RCT with parallel and crossover in the subgroup analysis, the results of the analysis using RCT with a parallel design were different from the crossover design (Figs. 5 and 6). However, the crossover design may not be appropriate for inclusion in this study, as the repeated bout effect has a significant long-lasting impact in susceptibility to EIMD. Moreover, not being able to control for blinding in

Table 4 CK

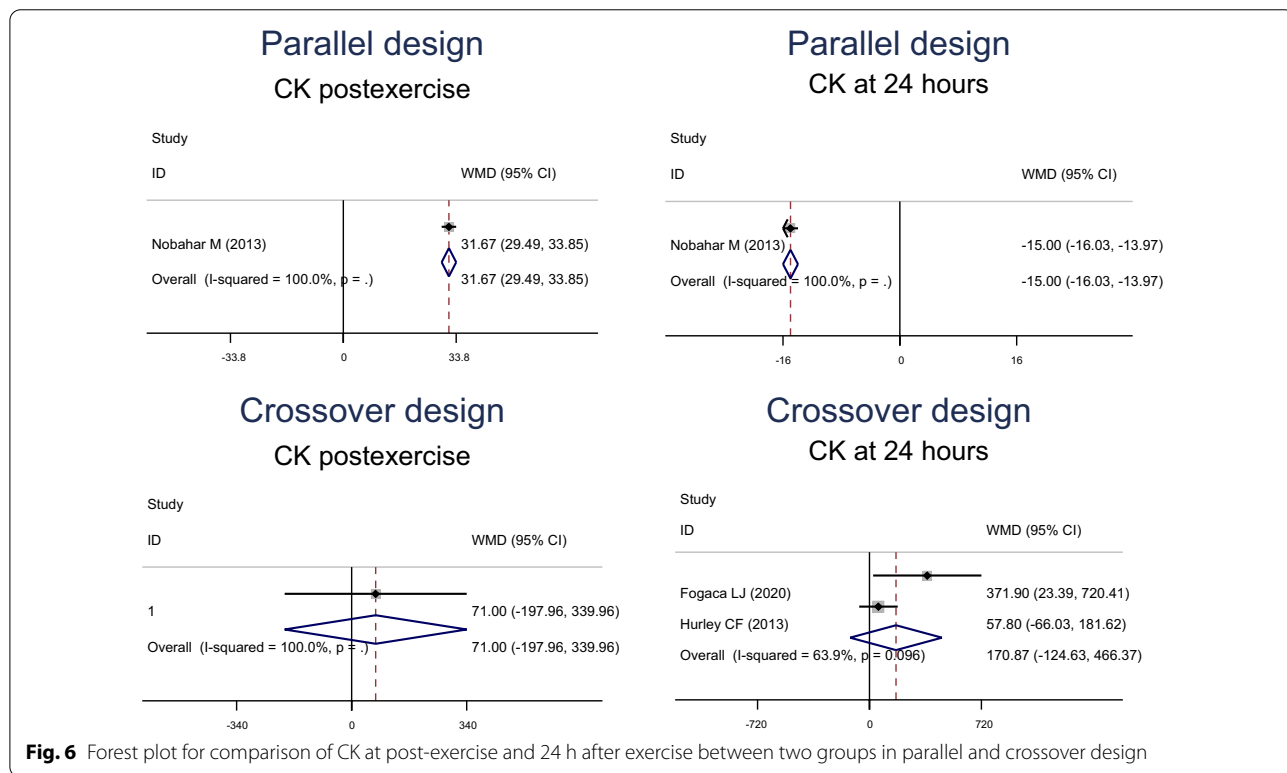
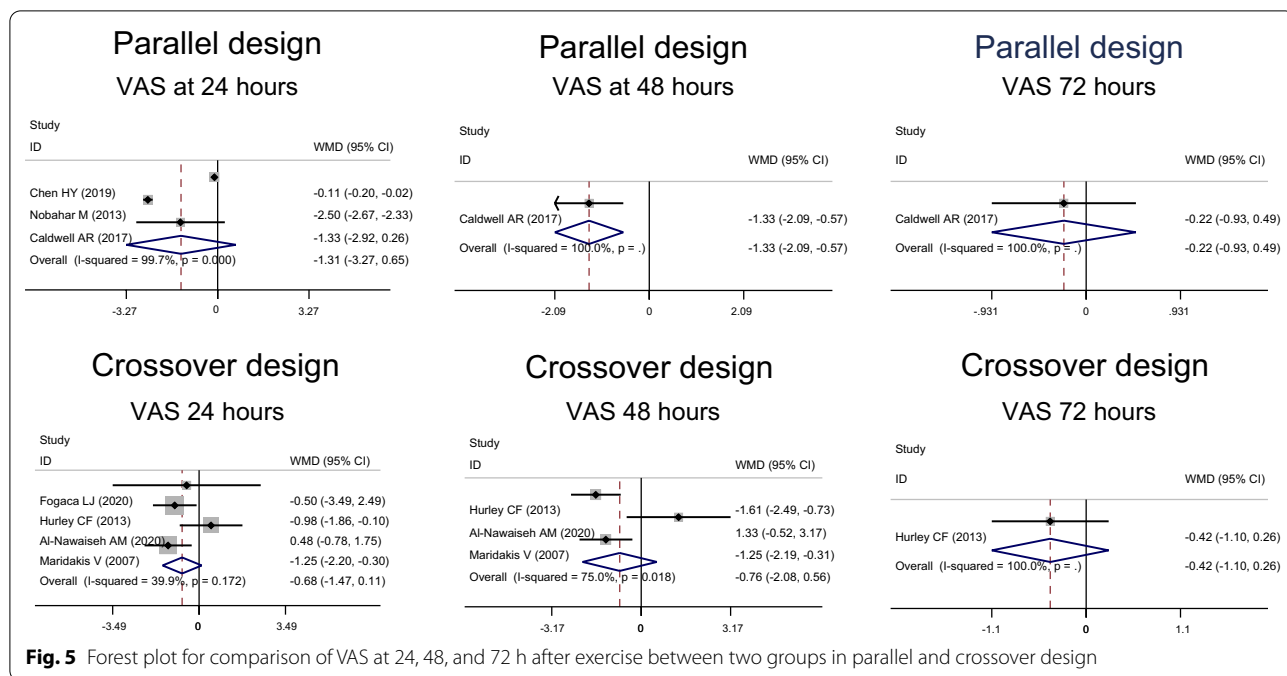
Author	Caffeine			Placebo		
	N	Mean	SD	N	Mean	SD
<i>A) CK Pre-exercise</i>						
Lorruama J	9	338.2	169.44	9	293.6	124.13
Caitlin F	9	106.183	44.355	9	107.527	59.14
Nobahar M	8	83.33		8	73.33	
UMD (95% CI)	3.72 (-41.84, 49.28)					
<i>B) CK Post-exercise</i>						
Lorruama J	9	476	122.73	9	405	392.96
Nobahar M	8	120	2.22	8	88.33	2.22
UMD (95% CI)	31.67 (29.50, 33.85)					
<i>C) CK at 24 h</i>						
Lorruama J	9	1097.6	123.45	9	725.7	518.97
Caitlin F	9	211.022	111.56	9	153.226	153.226
Nobahar M	8	111.67	1.05	8	126.67	1.05
UMD (95% CI)	49.84 (-73.13, 172.82)					



a systematic review involving supplementation strategies is a great concern. In this meta-analysis, we included all published studies comparing the effects of caffeine with a placebo because the amount of research that has been published to date is still relatively small. Therefore, we conducted a combined and subgroup analysis and found

that the study design did have an effect on the therapeutic use of caffeine.

Caffeine has a greater effect on resistance exercise than aerobic exercise in terms of reducing muscle soreness within 24 h. It is possible that despite inducing muscle soreness, aerobic exercises, such as cycling or



running, which increase the blood flow to the muscles, are better able to remove waste products and deliver nutrients to muscles (Tufano et al. 2012). Therefore, caffeine has no effect on this kind of exercise, but it is

effective in reducing muscle pain in people who perform resistance exercise. In the case of both research characteristics (parallel and crossover), there was no effect of caffeine. As the half-life of caffeine in the blood

stream is about 5 (1.5–9.5) hours, caffeine only stays in the bloodstream for a day (US 2001). In all crossover studies, seven-day intervals as a washout period were sufficient for the results to be the same as parallel studies.

The precise mechanism for the reduction in pain of caffeine is still uncertain. This is due to the fact that caffeine is a non-selective adenosine receptor antagonist with a high affinity for both A1 and A2A receptors. After 4–8 h following eccentric exercise, the expression of the gene for the adenosine A1 receptor in human skeletal muscle was increased by almost six times. Furthermore, adenosine A1 receptors have been implicated in the peripheral analgesic effects of adenosine in humans (Chen et al. 2003; Davis et al. 2003; Gaspardone et al. 1995; Motl et al. 2003; Sawynok 1998). Caffeine, which is an adenosine antagonist, has an effect on the activity of the central nervous system (CNS) because the adenosine receptors are blocked. This can result in decreased levels of muscle soreness (Hurley et al. 2013). In previous RCT studies, reduced feelings of pain and fatigue resulting from the adenosine antagonist action of caffeine have been demonstrated (Caldwell et al. 2017; Maridakis et al. 2007; Hurley et al. 2013; Fogaça et al. 2020). This is the first study that describes the reduced perception of soreness at 24–48 h post-exercise, without a difference in the CK level. Thus, we have found that there is a benefit of ingesting caffeine before the peak of DOMS (caffeine ingested at before exercise and 24 h after exercise). There were no significant differences in soreness levels between treatments after the third day of follow-up. The caffeine half-life is about 5 h after intake (Leonard et al. 1987). Therefore, small amounts of caffeine may remain in the body for 24 h. In terms of the CK level, exercises induce CK activity, with levels peaking between 24 and 48 h after exercise (Brancaccio et al. 2007; Schoenfeld 2012). This delay could be caused by oxidative stress, which is stimulated by lipid peroxidation, and can lead to membrane permeability, allowing muscle constituents such as CK to escape (Owens et al. 2019). In this study, caffeine did not influence CK activity after exercise.

This study has several strengths. First, this was the first meta-analysis that includes seven studies in the pooling of clinical outcomes of tests including caffeine supplement and placebo treatment groups. Second, we explored the possible causes of heterogeneity, when covariate data at baseline were available. Finally, publication bias for each outcome was assessed. However, there are also some limitations to this study. Its scope did not include other important outcomes such as adverse effects, other indirect markers (interleukin and tumor necrotic factor), functional outcomes (range of motion), and the effect of different caffeine levels, since there were incomplete data.

In addition, only English language publications were considered in this study.

Conclusions

To conclude, caffeine supplements reduce delayed-onset muscle soreness for caffeine supplements compared to a placebo 48 h after exercise. However, 24 h after exercise, caffeine may reduce DOMS only in people who have performed resistance exercise. The other marker (CK) used in this meta-analysis did not show any significant differences between the caffeine and placebo treatment groups. Further RCT studies should be performed to assess adverse effects of treatment, other indirect markers (IL and TNF), functional outcomes (range of motion), and the effect of different caffeine levels.

Abbreviations

DOMS: Delayed-onset muscle soreness; EIMD: Exercise-induced muscle damage; ROS: Reactive oxygen species; NF-κB: Nuclear factor-κB; ROM: Range of motion; CK: Creatine kinase; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCTs: Randomized controlled trial studies; VAS: Visual analog score; SD: Standard deviation; UMD: Unstandardized mean difference; BMI: Body mass index; CNS: Central nervous system.

Acknowledgements

All authors declare no funding source or sponsor involvement in the study design, collection, analysis and interpretation of the data, in writing the manuscript, and in submission of the manuscript for publication.

Authors' contributions

JM was responsible for the conception and design of research, collection of data, analysis and interpretation results of the data, preparing figure, and drafting manuscript. PK was responsible for the collection of research data and assembly of data. KC was responsible for manuscript writing, editing and revising manuscript for important intellectual contents, and final approval of the article. JK was responsible for the conception and design, supervising the analysis and interpretation of data, editing and revising manuscript, critical revision of the manuscript, and approving final version of manuscript and statistical expertise. All authors have read and approved the manuscript.

Funding

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Declarations

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Received: 28 June 2021 Accepted: 8 November 2021
Published online: 18 November 2021

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