The Influence of Caffeine Supplementation on Resistance Exercise: A Review

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The influence of caffeine supplementation on resistance exercise: a review

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Abstract

This paper aims to critically evaluate and thoroughly discuss the evidence on the topic of caffeine supplementation when performing resistance exercise, as well as provide practical guidelines for the ingestion of caffeine prior to resistance exercise. Based on the current evidence, it seems that caffeine increases both maximal strength and muscular endurance. Furthermore, power appears to be enhanced with caffeine supplementation, although this effect might, to a certain extent, be caffeine dose- and external load-dependent. A reduction in rating of perceived exertion (RPE) might contribute to the performance-enhancing effects of caffeine supplementation, as some studies have observed decreases in RPE coupled with increases in performance following caffeine ingestion. However, the same does not seem to be the case for pain perception, as there is evidence showing acute increases in resistance exercise performance without any significant effects of caffeine ingestion on pain perception. Some studies have reported that caffeine ingestion did not affect exercise-induced muscle damage but that it might reduce perceived resistance exercise-induced delayed onset muscle soreness; however, this needs to be explored further. There is some evidence that caffeine ingestion, compared to a placebo, may lead to greater increases in the production of testosterone and cortisol following resistance exercise. However, given that the acute changes in hormone levels seem to be weakly correlated with hallmark adaptations to resistance exercise, such as hypertrophy and increased muscular strength, these findings are likely of questionable practical significance. Although not without contrasting findings, the available evidence suggests that caffeine ingestion can lead to acute increases in blood pressure (primarily systolic), and, thus, caution is needed regarding caffeine supplementation among individuals with high blood pressure. In the vast majority of studies, caffeine was administered in capsule or powder forms, and therefore, the effects of alternative forms of caffeine such as chewing gums or mouth rinses on resistance exercise performance remain

unclear. The emerging evidence suggests that coffee might be at least equally ergogenic as caffeine alone when the caffeine dose is matched. Doses in the range of 3 to 9 $mg \cdot kg^{-1}$ seem to be adequate for eliciting an ergogenic effect when administered 60 min pre-exercise. In general, caffeine seems to be safe when taken in the recommended doses. However, at doses as high as 9 $mg \cdot kg^{-1}$ or higher, side-effects such as insomnia might be more pronounced. It remains unclear whether habituation reduces the ergogenic benefits of caffeine on resistance exercise, as no evidence exists for this type of exercise. Caution is needed when extrapolating these conclusions to females as the vast majority of studies involved only male participants.

Key points

- Caffeine supplementation may acutely enhance muscular endurance, maximal strength, and power in resistance exercise.
- Doses in the range 3 to 9 $mg \cdot kg^{-1}$ seem to be adequate for eliciting ergogenic effects. Caffeine seems to be generally safe when taken in these doses. However, at doses as high as 9 $mg \cdot kg^{-1}$ or higher, side effects might be more pronounced.
- Blood pressure may be increased following caffeine ingestion, and, therefore, caution is needed regarding caffeine supplementation among individuals with high blood pressure.
- The mechanism by which caffeine intake affects resistance exercise performance is likely multifactorial.

1 Introduction

Caffeine is one of the most commonly consumed drugs in the world [1], and a national survey indicated that 89% of American adults ingest caffeine with an average daily consumption (mean ± standard deviation) of 211 ± 472 mg [2]. This amount of caffeine is contained in approximately two cups of brewed coffee. Because of the ergogenic effects of caffeine on exercise performance, its use is also very prevalent among athletes [3]. Although several previous reviews have focused on the ergogenic benefits of caffeine on exercise performance [1, 4-11], none of them explicitly focused on resistance exercise. Therefore, there remains ambiguity regarding the effects of caffeine supplementation on resistance exercise.

Several muscular qualities are important when discussing resistance exercise, including muscular strength, muscular endurance, and muscular power. Muscular strength is ‘the capacity to exert force under a particular set of biomechanical conditions’ [12]. The following forms of muscular strength are usually assessed in research studies: dynamic strength (concentric actions coupled with eccentric actions), isometric strength (a muscle action in which the muscle-tendon complex does not change its length), and reactive strength (an ability to change quickly from eccentric to concentric muscle actions) [13]. A commonly used field-based test for assessing dynamic strength is the one-repetition maximum (1RM) test, while in laboratory settings dynamic strength is commonly assessed using isokinetic dynamometers [14]. Several neural factors such as motor unit recruitment, motor unit synchronization, rate coding, and neuromuscular inhibition underpin strength (a more detailed discussion of these factors can be found elsewhere [15]). Muscular endurance can be defined as ‘the ability of a muscle or muscle group to perform repeated contractions against a load for an extended period’ [16]. Muscular endurance is commonly assessed by performing repetitions of a given task to momentary muscular failure with a load corresponding to, for example, 50-60% of 1RM, or by measuring the time that a person is able to maintain force production at a given percentage of the force that corresponds to their maximal voluntary contraction (MVC). Muscular power denotes the rate of muscular work [17] and, in resistance exercise, it is commonly assessed by using linear position transducer(s) or a force plate [17].

There is a growing number of studies investigating the effects of caffeine supplementation on pain perception, ratings of perceived exertion (RPE), muscular qualities (e.g. maximal strength, muscular endurance and power), muscle damage and cardiovascular and hormonal responses to resistance exercise. However, given their mixed results, this paper aims to critically evaluate and thoroughly discuss the evidence on the topic and to provide practical guidelines for the application of caffeine supplementation when performing resistance exercise.

2 Possible mechanisms for the ergogenic effect of caffeine on exercise performance

Some of the initially-proposed mechanisms for the ergogenic effect of caffeine on exercise performance were enhanced fat oxidation and subsequent glycogen sparing [18]. However, these proposed mechanisms received little support in the literature, given that caffeine ingestion has been observed to be beneficial even in shorter duration exercise protocols (e.g., <30 minutes) in which glycogen levels do not appear to be a limiting factor [1]. These mechanisms also could not explain the observed ergogenic effects of caffeine on high-intensity, short-duration, anaerobic exercise performance [6]. Currently accepted mechanism(s) relate to the antagonistic effect of caffeine on adenosine receptors [19]. The binding of adenosine to A_1 and A_{2a} G protein-coupled receptors [19] inhibits the release of various neurotransmitters (such as acetylcholine and dopamine). Caffeine is structurally similar to adenosine, and, therefore, when ingested it blocks the binding of adenosine to the A_1 and A_{2a} receptors and promotes the release of these neurotransmitters [19]. Thus, caffeine exerts central nervous system effects and alters arousal, which may lead to improvements in performance [6]. Caffeine also increases calcium release from the sarcoplasmic reticulum and motor unit recruitment, which may result in a more forceful muscular contraction and help explain some of the ergogenic effects of caffeine on resistance exercise performance [20, 21]. Furthermore, studies conducted in both animals and humans suggest that caffeine may have a direct effect on the skeletal muscle tissue, which may, at least partially, explain the ergogenic effect of caffeine [22-24].

2.1 Effects of caffeine on ratings of perceived exertion

RPE is commonly assessed using the Borg 0-10, or the 6-20 point scale [25]. Caffeine may reduce RPE, which might allow an individual to perform more work with reduced subjective strain [20]. When assessed in an aerobic exercise setting, the reductions in RPE explain up to 29% of the ergogenic effect of caffeine on submaximal aerobic exercise performance [26], suggesting that a reduced RPE is a relevant factor in performance-increasing mechanisms.

Several studies observing a positive effect of caffeine on performance (e.g., acute increases in strength and muscular endurance) have also reported a reduction in RPE. For instance, Grgic and Mikulic [27] showed a 3% increase in 1RM barbell back squat performance and a corresponding 7% reduction in RPE (using the 6-20 point scale) with caffeine ingestion in a sample of resistance-trained individuals. Using a protocol that focused on muscular endurance, Duncan and Oxford [28] also reported a 13% decrease in RPE (using the 0-10 point scale) and an ergogenic effect of caffeine on muscular endurance. A subsequent study by Duncan et al. [29] confirmed these findings. However, the majority of the remaining studies have observed no significant effect of caffeine ingestion on RPE. For instance, Astorino et al. [30] did not find a reduction in RPE at doses of 2 and 5 $mg \cdot kg^{-1}$ of caffeine even though improvements in strength were evident with the 5 $mg \cdot kg^{-1}$ dose. Similarly, Duncan and Oxford [31] did not find a significant reduction in RPE ($p = 0.082$) when using a dose of 5 $mg \cdot kg^{-1}$ administered one hour before performing repetitions to momentary muscular failure with 60% 1RM on the bench press. Similar results have also been observed in other related studies [32-36]. While Arazi et al. [37] found that a dose of 2 $mg \cdot kg^{-1}$ is sufficient to achieve an RPE-reducing effect, this reduction in RPE was not accompanied by any increases in muscular strength or muscular endurance.

It can be hypothesized that exercise selection may determine the RPE response, given that complex, multi-joint exercises activate more muscle groups and, thus, require greater exertion. Two studies that did not observe a reduction in RPE used single-joint exercises, such as knee extensions and arm curls, which are less demanding than multi-joint exercises [34, 38]. While exercise selection might play a role in determining this effect, this hypothesis remains speculative as some studies using single-joint exercises reported a reduction in RPE following caffeine ingestion [38] and others using the bench press exercise (i.e., a multi-joint upper-body exercise) did not show significant reductions in RPE following caffeine ingestion [32, 35, 36]. Doherty and Smith [26] reported that RPE is lowered during prolonged aerobic exercise, but that it remains unaltered when assessed at exercise termination. Due to the nature of resistance exercise, RPE is evaluated almost exclusively at exercise termination, which might be a reason why studies have often reported no differences in RPE following caffeine ingestion. While a reduction in rating of perceived exertion might contribute to the performance-enhancing effects of caffeine, a firm conclusion cannot be made on this topic due to the inconsistent evidence presented in the literature.

2.2 Effects of caffeine on pain perception

Due to its blockade of adenosine receptors, caffeine is a common ingredient of over-the-counter medications for pain relief [39]. Resistance exercise may lead to significant acute increases in pain perception [40], which raises the possibility that a reduction in pain perception might contribute to the ergogenic effects of caffeine. Some studies have reported that caffeine ingestion decreases pain perception but without any significant effects on performance [27, 37]. Tallis and Yavuz [41] and Sabblah et al. [42] did not observe any significant reductions in pain perception, although caffeine ingestion increased muscular strength, suggesting that factors other than the reduced perception of pain contributed to the ergogenic effect. Although two studies reported that improvements in performance were accompanied by a decrease in pain perception [28, 29], there was also a decrease in RPE that made it difficult to determine exactly what contributed to the ergogenic effect. Based on the current evidence, it seems that mechanism(s) other than reductions in pain perception contribute to the enhanced resistance exercise performance with caffeine ingestion.

3 Effects of caffeine on strength

3.1 1RM strength

Some of the initial studies that investigated the effects of caffeine on 1RM dynamic strength did not show a significant ergogenic effect. For instance, Astorino and colleagues [43] did not find any performance-enhancing effects of caffeine ingestion on 1RM strength in the bench press and leg press exercises among resistance-trained men. However, a study by Goldstein et al. [44], involving resistance-trained women, showed that caffeine ingestion may significantly improve upper-body 1RM as assessed by the bench press exercise.

A prevalent issue among individual studies examining the effects of caffeine supplementation on resistance exercise performance is the use of small sample sizes [45], which may result in low statistical power. To better understand the equivocal evidence reported in the literature, Grgic et al. [46] recently conducted a meta-analysis of studies assessing the impact of caffeine on 1RM muscular strength. The findings of this review suggested that caffeine ingestion enhances 1RM muscular strength compared to placebo (Fig. 1). Subgroup analyses revealed that caffeine ingestion increased upper- but not lower-body strength. The raw difference between the mean effects of placebo and caffeine in the subgroup analysis equated to 3.5 kg (95% confidence interval [CI]: 1.5, 4.8 kg) and 1.7 kg (95% CI: -1.7, 5.0 kg) of lifted weight for the upper-body and the lower-body, respectively. From a physiological perspective, there appears to be no rationale as to why caffeine would increase upper- but not lower-body strength. In fact, as we discuss below (section 3.2), due to the differences between the upper- and lower-body in the amount of muscle mass involved, the opposite results might be expected. That said, the subgroup analyses for lower- and upper-body strength were limited as they included only seven and eight studies, respectively. While the meta-analysis provided some evidence that caffeine increases 1RM strength, given the relatively small number of studies investigating this topic, future research is warranted.

*****Insert Fig. 1 about here*****

3.2 Isometric and isokinetic strength

Using a model focused on the dorsiflexor muscles, Tarnopolsky and Cupido [47] reported no significant effect of caffeine ingestion on enhancing MVC. However, in an experiment performed by Park et al. [48] that focused on the knee extensor muscles, caffeine led to significant increases (+10%) in MVC compared to a placebo. Some of these findings can possibly be attributed to differences in the activation of smaller versus larger muscle groups. Indeed, a meta-analytic review by Warren et al. [49], which pooled MVC tests (with the majority of studies using isometric tests of strength), reported that caffeine ingestion may significantly increase MVC by ~4%. However, this effect seemed to be evident primarily in the knee extensor muscles (+7%) and not in smaller muscle groups, such as the dorsiflexors.

During a MVC, the activation of the knee extensor muscles is usually lower when compared with other muscle groups [49, 50]. For instance, smaller muscles such as the tibialis anterior can be activated up to 99% of their maximum during a MVC and, hence, the activation of these muscles is already at near-maximal level [51, 52]. However, knee extensor activation is usually 85 to 95% of its maximal activation and, therefore, Warren et al.'s hypothesis was that with caffeine ingestion, the muscle activation in this muscle group can be enhanced, which in turn can augment the MVC [49]. Caffeine ingestion has been reported to increase cortical and spinal neuron excitability [53], which might increase muscle activation through an increase in motor unit recruitment. Indeed, Black et al. [54] demonstrated that caffeine ingestion enhances MVC and motor unit recruitment in the knee extensors but not in the elbow flexors, supporting the hypothesis by Warren et al. [49].

Recently, Tallis and Yavuz [41] reported that caffeine ingestion enhanced isokinetic strength in the knee extensors but not in the elbow flexors, adding to the evidence showing that benefits of supplementation might be related to the different activation of smaller versus larger muscle groups. The results by Tallis and Yavuz [41] for isokinetic strength were confirmed in a recent meta-analysis [55], whereby the pooled relative effect size from ten included studies was 0.16 (+6%), suggesting that caffeine ingestion enhances isokinetic strength. However, again, this effect was not observed in smaller muscle groups such as the elbow flexors and was predominately manifested in the knee extensors.

In summary, the current evidence suggests that caffeine ingestion may have an ergogenic effect on muscular strength across all muscle action types [56]. As such, these findings are likely to have the highest application in sports such as powerlifting and weightlifting. However, studies conducted specifically among competitive powerlifters and weightlifters are needed, given that most of the previous studies included untrained or recreationally trained individuals. More evidence is needed to examine the differences between small and large muscle groups, as well as between the upper- and lower-body musculature. Although it seems that caffeine enhances MVC, isometric actions and isokinetic apparatuses are used to a lesser degree in traditional resistance exercise routines, which somewhat limits the practical application of these findings.

4 Effects of caffeine on muscular endurance

Several individual studies [28, 29, 32] and meta-analytic reviews [49, 57] show that caffeine (most commonly administered in a dose of 5 to 6 mg·kg^{-1}) can have an ergogenic effect on muscular endurance, with improvements found for both the upper-body [28] and the lower-body [29] musculature. Forest plots in the reviews conducted by Polito et al. [57] and Warren et al. [49] indicate that studies almost never show that caffeine produces an ergolytic effect on muscular endurance performance. Specifically, in the work by Warren et al. [49], out of the 23 studies included in the meta-analysis, sample effect sizes for only four studies [53, 58-60] favored the placebo group. The effect sizes in these four studies ranged from -0.32 to -0.03, but none were statistically significant. In the review by Polito et al. [57], none of the studies favored placebo. The pooled effect sizes in these reviews ranged from 0.28 to 0.38, that is, +6% to +7%. The raw difference between mean effects of placebo and caffeine for the number of completed repetitions in the studies included in the Polito et al. [57] review ranged from -0.3 to +6 repetitions. In the studies identified by Warren et al. [49], the time to maintain an isometric contraction at a given percentage of MVC (a test used to assess muscular endurance) with caffeine ingestion ranged from 8 to 32 s. Future long-term studies are needed to explore if these small acute increases in performance also impact long-term adaptations to resistance exercise.

Limited evidence also shows an ergogenic effect of caffeine on muscular endurance in a sleep-deprived condition (6 hours of sleep or less) [61]. Several studies that carried out muscular endurance assessments following maximum strength testing did not observe a significant ergogenic effect of caffeine on muscular endurance [27, 43, 44], suggesting that caffeine supplementation may not be as effective on muscular endurance as fatigue develops. These results seem surprising given that caffeine ingestion has been shown to slow down the fatigue-induced loss of force production [62]. Caffeine ingestion should, therefore, theoretically be ergogenic even in the presence of fatigue and the exact reasons for the lack of an ergogenic effect of caffeine in the referenced studies remain unclear. Studies that investigated the effects of caffeine supplementation on muscular endurance among females also did not show a significant performance-enhancing effect [37, 42, 44]; albeit, with sample sizes of 15, 10, and eight participants, respectively. Phases of the menstrual cycle might play an important role in studies involving women given that caffeine clearance is slower in the luteal phase of the cycle [63]. Furthermore, the use of oral contraceptives may alter caffeine metabolism [64], which also needs to be considered when conducting studies among women. This topic seems to be under-investigated in this population and requires further attention. In summary, it seems that caffeine can acutely enhance muscular endurance, but details such as fatigue-related and sex-specific responses require future study to better determine its effectiveness.

5 Effects of caffeine on power

Most of the studies on power outcomes focused on variations of jump performance [46], power recorded during the Wingate 30-s test [65], or repeated and intermittent-sprints performance [66, 67]. Caffeine may acutely enhance these components of power [46, 65-67], but there is limited research on the effects of caffeine on power expression measured as contraction velocity during traditional dynamic resistance exercises. In a study by Mora-Rodríguez et al. [68], 12 trained men performed three exercise trials: (i) a morning training session (10:00 a.m.) after the ingestion of 3 $mg \cdot kg^{-1}$ of caffeine, (ii) a morning training session after ingesting a placebo, and (iii) an afternoon session (18:00 p.m.) following the ingestion of a placebo. Bar displacement velocity was measured during the squat and bench press exercises with loads that elicited a bar velocity of 1 $m \cdot s^{-1}$ and with a load corresponding to 75% of 1RM. Results showed that power increased with all loads with caffeine ingestion, except for the bench press velocity at 1 $m \cdot s^{-1}$ ($p = 0.06$, Cohen's $d = 0.68$). Using the same dose of caffeine in a group of 14 Brazilian jiu-jitsu athletes, Diaz-Lara et al. [69] confirmed that caffeine may be ergogenic for power, showing an increase in maximal power and mean power in the bench press exercise.

Pallarés et al. [70] sought to investigate contraction velocity at three different doses of caffeine (i.e., 3, 6, and 9 $mg \cdot kg^{-1}$) and across four different loading schemes, namely, 25%, 50%, 75%, and 90% of 1RM performed using the bench press and barbell back squat exercises. When measured at loads of 25% and 50% of 1RM, all doses of caffeine resulted in increased power in both exercises. At higher loads, higher doses seem to be needed to augment power, both in the bench press and in the squat exercises. These results suggest that greater doses of caffeine might be warranted for a performance-enhancing effect when exercising with higher loads. Such large doses of caffeine also seem to generate more side effects [70], which also needs to be considered. In the same sample, caffeine has been shown to have a more pronounced effect on power when administered in the morning versus in the afternoon hours [71]. Such results could be due to the reduced capacity to activate/recruit the musculature in the morning hours [71]. Therefore, when administered in the morning, caffeine may augment the ability to activate/recruit the musculature [71]. Also, side effects such as insomnia may be even more prevalent when supplementing with caffeine in the afternoon hours [71], which does highlight that time-of-day is an important variable to consider when prescribing caffeine supplementation.

It seems that caffeine may enhance contraction velocity, although this finding is based only on the results from a few studies. Given some of the mixed evidence presented for maximal strength, this might indicate that caffeine has a more pronounced effect on contraction velocity than on maximal force production. Future studies should consider examining changes in both 1RM strength and contraction velocity (with lower loads) in the same group of participants to investigate if this is indeed the case. The limited research to date suggests that caffeine ingestion may acutely increase muscle power in resistance exercise and, therefore, athletes competing in events in which power is a significant performance-related variable might consider using caffeine supplementation pre-exercise.

6 Effects of caffeine on muscle damage and delayed onset muscle soreness

6.1 Delayed onset muscle soreness

Resistance exercise may lead to exercise-induced muscle damage and delayed onset muscle soreness (DOMS) [72]. Exercise-induced muscle damage commonly brings about DOMS, which can be defined as the pain felt upon palpation or movement of the affected tissue [73]. DOMS appears within a few hours post workout, peaks 1 to 3 days following the exercise session, and can last up to 10 days [74]. Because caffeine is an adenosine antagonist, its consumption might increase the response of the sympathetic nervous system, and, thus, decrease the perception of muscle soreness [75].

Two of the initial studies [38, 76] that investigated the effects of caffeine ingestion on DOMS following resistance exercise observed that caffeine might indeed reduce DOMS. Hurley et al. [38] employed a training protocol that consisted of five sets of biceps curls exercise performed with a load corresponding to 75% of 1RM. On days 1 to 5, the participants were required to assess their levels of soreness on three different scales: overall soreness, overall fatigue, and soreness on a palpation scale. Administration of caffeine (5 mg·kg^{-1}) allowed the participants to perform a significantly greater number of repetitions during the fifth set of bicep curls. However, despite greater total work performed following caffeine ingestion, the overall perception of soreness was significantly lower on day 2 and day 3 with caffeine ingestion as compared to placebo. Because soreness peaks 1 to 3 days following exercise, the results of this study indicate that caffeine can significantly reduce the perception of soreness following resistance exercise. Hurley et al. [38] also assessed creatine kinase levels and, consistent with the results of Machado et al. [77] (see section 6.2), they reported that caffeine ingestion did not significantly affect creatine kinase levels.

In the Maridakis et al. [76] study, during the first visit (no supplement ingestion), the participants underwent an electrically-stimulated eccentric exercise of the quadriceps that consisted of 64 eccentric actions; a protocol known to bring about DOMS [78]. Twenty-four and 48 hours following the protocol, the participants consumed either a placebo or caffeine (5 $mg \cdot kg^{-1}$) in a counterbalanced fashion and expressed their perceived levels of soreness after performing an MVC and a submaximal eccentric test. The results showed that with the ingestion of caffeine there was a significant reduction in DOMS with a greater effect observed during the MVC as compared to submaximal eccentric movements. In a recent study, Green et al. [79] showed that caffeine increased peak torque but did not impact the perception of soreness in a group of 16 participants using a caffeine dose of 6 $mg \cdot kg^{-1}$. While Maridakis et al. [76] used a protocol that involved maximal and submaximal eccentric movements, the protocol in this study for assessing DOMS involved expressing subjective levels of soreness after stepping down from a box [80], which might explain the differences in results between the studies. The use of different methods for assessing DOMS somewhat limits the comparison of results between the studies.

In summary, there is some preliminary evidence to suggest that caffeine ingestion may indeed reduce DOMS, which is not surprising given that caffeine can have a hypoalgesic effect. That said, given the small number of studies, further research exploring this topic is warranted. The studies that have been conducted so far mostly administered caffeine only pre-exercise. However, Caldwell et al. [81] recently explored the effects of ingesting caffeine on perceived soreness in the days following exercise (i.e., a 164 km endurance cycling event). Given that the authors reported positive effects of caffeine on relieving feelings of soreness during the three days of recovery post-exercise, this is an area that could be further explored in resistance exercise as well.

6.2 Muscle damage

Machado et al. [77] investigated the effects of caffeine ingestion on blood markers of muscle damage, including creatine kinase, lactate dehydrogenase, alanine aminotransferase, and aspartate aminotransferase. Fifteen participants took part in a resistance exercise protocol consisting of six exercises performed in three sets of ten repetitions. The caffeine dose was 4.5 $mg \cdot kg^{-1}$. All the abovementioned markers of muscle damage increased after the resistance exercise session with no significant differences found between the caffeine and placebo conditions. In this study, researchers equated the total work (calculated as load × sets × repetitions) between the caffeine and placebo sessions. However, given that caffeine may enhance acute exercise performance, this might consequently lead to greater increases in markers of muscle damage. This hypothesis could be explored in future studies that do not equate the total work between the caffeine and placebo trials.

7 Effects of caffeine on hormonal responses

Acute increases in hormones such as testosterone (a primary anabolic hormone), cortisol (a systemic catabolic marker), and growth hormone (a hormone associated with reproduction and stimulation of cellular growth) following resistance exercise have received considerable attention in the literature [82]. It has been suggested that acute changes in these hormones influence resistance training adaptations such as muscular hypertrophy and increases in strength [82]. However, others recently found that the acute changes in hormones are weakly correlated with long-term adaptations to resistance training [83]. Thus, although some studies [35, 84-86] reported that caffeine ingestion, as compared to placebo, may lead to greater increases in the production of testosterone and cortisol following resistance exercise (even when the workload is matched between the conditions), the practical applicability of these findings remains unclear.

8 Effects of caffeine on muscle protein synthesis and anabolic signaling

One of the hallmark adaptations to resistance exercise is muscular hypertrophy. In general, it is accepted that the anabolic mammalian mechanistic target of rapamycin complex 1 (mTORC1) signaling cascade mediates muscular hypertrophy which is a cumulative result of acute increases in protein synthesis above protein degradation (i.e., net protein accretion) [87, 88]. Some of the studies conducted in cultured cells have observed that caffeine inhibited mTOR activity [89, 90], albeit, such effects were seen at supra-physiological concentrations of caffeine. A recent study by Moore et al. [91] conducted in mice (with physiological concentrations of caffeine that would be observed in humans following moderate caffeine intake), showed that caffeine did not negatively affect mTOR activity or muscle protein synthesis after a bout of electrically-stimulated contractions. Moreover, caffeine even enhanced the phosphorylation of ribosomal protein S6 suggesting a positive effect of caffeine on anabolic signaling. Furthermore, work on rats in the same study showed that caffeine did not affect plantaris muscle hypertrophy [91]. While cell culture and animal models may provide some interesting findings, they also may have limited relevance to humans. Currently, there are no published studies examining the effects of caffeine on muscle protein synthesis and anabolic signaling in response to resistance exercise in humans. While there are some unpublished observations involving resistance-trained men in whom caffeine ingestion did not negatively affect muscle protein synthesis responses following resistance exercise [92], these results remain to be published. Therefore, this is an interesting area that could be explored in future research.

9 Effects of caffeine on cardiovascular responses

9.1 Blood pressure

Even under resting conditions, caffeine ingestion of 250 mg has been shown to increase blood pressure [93]. Also, resistance exercise may lead to significant acute increases in systolic and diastolic blood pressure [94]. Therefore, it is possible that the combination of this type of exercise with caffeine ingestion might augment acute blood pressure responses.

Only a few studies to date have focused on the effects of caffeine on the cardiovascular system in resistance exercise. Jacobs and colleagues [59] initially reported that the ingestion of caffeine did not increase systolic blood pressure more than the ingestion of placebo during a resistance exercise session consisting of three supersets (leg press exercise followed by the bench press exercise). Following caffeine ingestion, Astorino et al. [95] reported increases in systolic but not diastolic blood pressure. In a study including normotensive and hypertensive men, Astorino et al. [96] confirmed their initial findings by showing that caffeine ingestion increases resting, exercise, and recovery systolic blood pressure. The same effect on blood pressure was observed in a study by Goldstein et al. [44], in which the ingestion of caffeine led to an increase in systolic blood pressure by 4 mmHg. Comparable results were observed by others as well [35]. When ingested before physical activity, caffeine may reduce myocardial blood flow during exercise [97]. This reduction in blood flow likely explains the augmented increases in blood pressure that may occur with the ingestion of caffeine in resistance exercise [97].

Passmore et al. [98] have reported that caffeine doses of 45, 90, 180, and 360 mg increase blood pressure in a dose-response fashion (i.e., greater increases with higher doses). Therefore, the discrepancy in findings between studies of subjects participating in resistance exercise might be explained by the caffeine dose, as Jacobs et al. [59] used a dose of 4.5 $mg{\cdot}kg^{-1}$, while Astorino et al. [95] and, subsequently, Goldstein et al. [44], used a dose of 6 $mg{\cdot}kg^{-1}$. Although variations in dosage might help explain these findings, it is important to highlight that a caffeine dose of 4 $mg{\cdot}kg^{-1}$ was reported to increase blood pressure [99]. Furthermore, in some studies, a dose of 5 $mg{\cdot}kg^{-1}$ did not result in greater increases in blood pressure over placebo alone, highlighting the equivocal nature of research done in this area [36]. Factors such as participants' posture, arm support, arm position, left or right-hand side, cuff, and empty/full bladder are all known to influence blood pressure estimates [100]. However, most of the studies only reported the timing of measurement and posture, making the between-study comparison of the results difficult. Due to the effects of caffeine on blood pressure, this supplement might not be recommendable for individuals with high blood pressure, as it may result in excessive cardiovascular demands [101]. Therefore, caution is needed when considering caffeine supplementation in these populations.

9.2 Heart rate

Besides blood pressure, heart rate is another important cardiovascular variable that needs to be considered. Astorino et al. [95] also evaluated heart rate responses in a cohort of resistance-trained men performing 1RM and muscular endurance tests on both the bench press and leg press exercises. They observed that heart rate before starting the exercise bout and pre- bench-press increased by ten beats per min with the ingestion of caffeine. While some studies observed similar effects of caffeine on this variable [33, 34, 102], others have reported no differences in heart rate responses between the caffeine and placebo conditions [28, 32, 35, 36, 96, 99]. Some discrepancies between the studies might be related to the habitual caffeine intake of participants. Specifically, there is evidence to suggest that increases in heart rate with caffeine ingestion are exacerbated in individuals who habitually consume lower amounts of caffeine as compared to high habitual users [103, 104]. However, while some studies did not assess habitual caffeine intake [28, 33], the participants in others reported a wide range of habitual caffeine intake varying from 30 to 600 mg [95]. Given these limitations, future studies should consider exploring potential differences in the effects of caffeine ingestion on heart rate responses in resistance exercise between low and high habitual caffeine users. Future work is warranted on the effects of caffeine on heart rate variability (time differences between consecutive heartbeats) in resistance exercise, as there is evidence (in other forms of exercise) that caffeine ingestion may negatively impact this outcome [105].

10 Caffeine form

The most common forms of caffeine administration for supplementation purposes are capsules and powder mixed with liquid. Currently, there is a growing interest in investigating the effects of caffeine administered in alternative forms such as chewing gums, bars, gels, mouth rinses, energy drinks, and aerosols [11]. Some of these forms of caffeine may have a faster absorption rate, which might be of interest in many sporting situations [11]. For instance, Kamimori et al. [106] observed that the time to reach maximal caffeine concentration in the blood was 44 to 80 min with caffeine administered in chewing gum, while in the capsule trials this time amounted to 84 to 120 min. Pharmacokinetics of different forms of caffeine are discussed in more detail in a recent paper by Wickham and Spriet [11]. For resistance exercise protocols only three studies have been conducted with alternative forms of caffeine. One study explored the effect of caffeine mouth rinse on muscular endurance and reported no significant increases in volume load with caffeine ingestion [107]. This can probably be explained by the observation that caffeine administered in this form does not increase blood caffeine concentration [108]. Another study investigated the effects of a sugar-free drink containing a fixed dose of 160 mg of caffeine and a placebo beverage on 1RM bench press performance and upper-body muscular endurance [109]. No significant increases in either strength or muscular endurance were found following caffeine ingestion. Some unpublished observations suggest that consumption of caffeinated chewing gum (fixed dose of 75 mg of caffeine) can increase 1RM squat performance [110]. However, the study has yet to be published, which precludes its scrutinization. This area of research is currently in its infancy and needs further exploration.

Researchers have only recently begun to compare the effects of caffeine alone and caffeinated coffee using a resistance exercise protocol. The first study that examined this matter was conducted by Trexler et al. [111]. The authors investigated the effects of: (i) caffeine administered in an absolute dose of 300 mg, (ii) coffee with a dose of 303 mg of caffeine, and (iii) a placebo. The effects of coffee on 1RM leg press exercise performance were greater than the effects of caffeine ingestion. The second study that investigated this topic in relation to resistance exercise is the work by Richardson and Clarke [102] who tested muscular endurance in the squat exercise. Results showed that both caffeinated coffee and decaffeinated coffee plus 5 mg·kg^{-1} of anhydrous caffeine resulted in significantly better squat exercise performance compared to other conditions. Therefore, notwithstanding the lack of studies conducted in this area, based on the current evidence, it may be inferred that both coffee and caffeine anhydrous are suitable pre-workout options, while the choice would be a matter of personal preference.

11 Caffeine dose, timing, and habitual intake

The most commonly used dose of caffeine in studies examining the effects of caffeine on exercise performance is 6 mg·kg^{-1} [1]. This dose is relatively high, as, for an 85-kg individual, it equates to the amount of caffeine in approximately four to five cups of coffee. As discussed elsewhere [10], there is a growing interest in investigating the effects of lower doses of caffeine (i.e., ≤3 mg·kg^{-1}) on exercise performance as these doses may still lead to improvements in alertness and mood during exercise and are associated with few, if any, side effects [10].

Astorino et al. [30] reported that performance of the knee extension and flexion exercises was significantly improved with a 5 mg·kg^{-1} dose of caffeine. However, no improvement in performance was observed with a 2 mg·kg^{-1} dose. Using the same doses, Arazi et al. [37] observed that caffeine did not improve leg press strength and muscular endurance at either 2 or 5 mg·kg^{-1} doses. Tallis and Yavuz [41] observed that both 3 and 6 mg·kg^{-1} caffeine doses were effective for increasing lower-body strength. Furthermore, as stated earlier when discussing power outcomes (section 5), three studies [68-70] have investigated the effects of 3 mg·kg^{-1} of caffeine on resistance exercise performance and power and suggested that this dose can be ergogenic. However, at specific external loads, a higher dose was needed to achieve an increase in performance. A meta-regression by Warren et al. [49] suggested that there is a dose-response relationship between the doses of caffeine and the magnitude of the effects on muscular endurance. Specifically, for an increase in caffeine dose of 1 mg·kg^{-1} muscular endurance effect size increased by 0.10. However, optimal doses of caffeine still need to be further explored in resistance exercise protocols and other sport and exercise settings [22]. Starting with a lower dose (such as 3 mg·kg^{-1}) may be a good initial option; the doses can be adjusted after that according to the individual responses.

As with the caffeine dose, the optimal timing of caffeine supplementation has been under-investigated. Caffeine has a half-life of 4 to 6 hours, and its plasma concentration reaches maximum approximately one hour after ingestion (although this can depend on the source of caffeine and can vary considerably between individuals) [4, 112]. Therefore, in most studies, the exercise session begins one hour after the supplement is ingested. Instead of the common 60-min waiting time, some studies have used a 45-min [45] or a 90-min [59] waiting time and did not show performance-enhancing effects of caffeine. However, it remains unclear if the waiting time was responsible for the lack of a significant effect. This might have been a consequence of other factors, such as small sample sizes, as the studies included nine and 13 participants, respectively [45, 59]. Also, genetic differences in caffeine metabolism among the participants (as discussed in section 12) may have contributed to the outcomes. Because of the lack of studies, the optimal timing of caffeine intake for resistance exercise remains unclear. Nevertheless, it is well-established that ergogenic effects can be seen one hour post ingestion when using capsule or powder forms of caffeine [46, 49, 55, 57].

There is limited research regarding the influence of habitual caffeine intake and the acute effects of caffeine supplementation on exercise performance. Based on the available evidence, it does not seem that habitual caffeine ingestion reduces the ergogenic benefits of acute caffeine supplementation [47, 103, 113-116]. However, there are some contrasting findings [117, 118] suggesting that non-habitual caffeine users experience a greater magnitude of the ergogenic effect with caffeine supplementation compared with caffeine habitual users. Some limitations of these studies include that Bell and McLellan [117] did not report if the questionnaire they used for assessing habitual caffeine intake had previously been validated while Evans et al. [118] used a dose of caffeine that was relatively small (on average, 2.5 mg·kg^{-1}; ~200 mg vs. 3 to 6 mg·kg^{-1} in most other studies). It might be that habitual consumers need more caffeine to achieve the same ergogenic effect as low habitual users.

Gonçalves et al. [113] explored this topic in a large sample (*n* = 40) grouped into tertiles representing low, moderate, and high habitual caffeine users, where the habitual caffeine intake was assessed using a previously validated questionnaire. This study suggested that habitual caffeine intake does not cancel out the performance benefits of the acute supplementation with caffeine. However, this study used a 30-min cycling time trial test and given that there is no research done in this area using resistance exercise protocols, this remains an important avenue for future research.

Additional factors such as ingestion of caffeine in a fed vs. fasted state are important to consider given that the absorption of caffeine is slower in a fed state [19]. Indeed, a dose of 3 mg·kg^{-1} of caffeine administered 60-90 min pre-exercise has been shown to be ergogenic in a fasted [119] but not in a fed state [120]. Additionally, withdrawal is another variable to consider given that habitual caffeine users may experience headache and increased irritability after caffeine abstinence of 24 hours [121]. These symptoms may confound the study design, because the performance under the placebo condition may be impaired due to the withdrawal effects [19].

12 Genetic differences in responses to caffeine ingestion

There is a substantial inter-individual variability in responses to caffeine ingestion [122]. While some individuals experience enhanced performance, others show no improvement, and, in some cases, even performance decrements [122]. Based on some recent evidence it seems that genotype might play an important role in the inter-individual variability in responses. The initial studies that explored the genetic differences in responses to caffeine ingestion while using an exercise protocol report mixed findings [123-125]. For instance, Womack et al. [123] reported a greater effect of caffeine on exercise performance in AA than in C allele carriers while others found no significant effect of this polymorphism on caffeine's ergogenic effect [125]. Most of these studies had small to moderate sized samples (n = 16 to 35). However, in a large cohort of male athletes (n = 101), Guest et al. [126] showed that the individuals with the AA genotype had a 5% and 7% improvement in time trial performance with the ingestion of 2 mg·kg^{-1} and 4 mg·kg^{-1} of caffeine, respectively. Individuals with the AC genotype did not improve performance following caffeine supplementation, and those with the CC genotype experienced decreases in performance after the ingestion of caffeine. Recently, Rahimi [127] assessed the effects of caffeine ingestion on muscular endurance using a resistance exercise protocol. A significant difference was observed between the groups for the total number of performed repetitions following caffeine ingestion (AA = +13% vs. AC/CC = +1%; p = 0.002). While this is the only study that examined this topic using a resistance exercise protocol, it does provide compelling evidence in support of the importance of considering genotype when assessing the response to caffeine ingestion.

13 Placebo effects of caffeine supplementation

Pollo et al. [128] investigated the placebo effect on leg extensions exercise performance and reported that the administration of a placebo, alongside the suggestion that it was caffeine, increased mean muscle work and decreased self-perceived muscle fatigue. Duncan et al. [129] confirmed the findings by Pollo et al. [128] as their results showed that the participants were able to perform two more repetitions under the perceived caffeine condition, and this was accompanied by a reduced RPE, thereby highlighting the power of a placebo for driving positive effects on exercise outcomes [130].

In their proof-of-principle study, Saunders et al. [131] reported that the participants who correctly identified placebo experienced possible harmful effects on performance. Furthermore, those who thought that they ingested caffeine while ingesting placebo also appeared to improve their performance. Therefore, to investigate if any performance-enhancing effects are undoubtedly related to caffeine ingestion or merely a placebo effect, it would be of importance to ask the participants to indicate which trial they perceived to be the caffeine trial. Unfortunately, this question was not asked in several studies examining the effects of caffeine on resistance exercise [27, 32, 36, 44, 45] and the results of such studies therefore need to be interpreted with caution. Although not in all cases, some studies that investigated the effectiveness of the blinding indicated that blinding of the participants is effective, as only 29% to 60% of the participants correctly identified the caffeine trials [29, 43, 132]. It is interesting that in the Bond et al. [58] study, there was no blinding of the participants or the investigators, yet, no effect of caffeine on performance was seen (the percent changes and effect sizes actually favored the placebo trial). Furthermore, in the work by Tallis et al. [133] an equal improvement in peak concentric force was found in the trial in which the participants were told that they were given caffeine and did indeed receive a caffeine dose, and in the trial in which the participants were told that they were given placebo even though they received caffeine. These results seem encouraging as they reflect the true effect of caffeine supplementation on performance. Nonetheless, future research is necessary to differentiate between the actual effects of caffeine and placebo effects.

14 Conclusions

Current evidence suggests that caffeine ingestion increases maximal strength, as assessed by 1RM and MVC tests, and muscular endurance. Furthermore, studies show that power is enhanced by caffeine supplementation, although this effect might be caffeine dose- and external load-dependent. While a reduction in RPE potentially contributes to the performance-enhancing effects of caffeine supplementation, the same was not found for pain perception. Some studies have reported that caffeine ingestion did not affect exercise-induced muscle damage but that it might even reduce resistance exercise-induced DOMS. There is some evidence that caffeine ingestion, as compared to placebo, leads to greater increases in the production of testosterone and cortisol following resistance exercise. However, given that the acute changes in hormone levels are weakly correlated with long-term adaptations to resistance exercise, such as hypertrophy and increased muscular strength, these findings are likely of questionable practical significance.

Although not without contrasting findings, the available evidence suggests that caffeine ingestion can lead to acute increases in blood pressure (primarily systolic), and, thus, caution is needed regarding caffeine supplementation among individuals with high blood pressure. In the vast majority of studies, caffeine was administered in capsule or powder forms, and the effects of alternative forms such as chewing gums or mouth rinses on resistance exercise performance therefore remain unclear. The emerging evidence suggests that coffee is at least equally ergogenic as caffeine alone when the caffeine dose is matched. Nevertheless, more research is needed on this topic. Doses in the range 3-9 $mg \cdot kg^{-1}$ seem to be adequate for eliciting an ergogenic effect when administered 60 min pre-exercise. It remains unclear what the minimal effective doses are for different types of resistance exercise.

In general, caffeine was found to be safe when taken in the recommended doses. However, at doses as high as 9 $mg \cdot kg^{-1}$ or higher, side-effects such as insomnia are more pronounced, which needs to be considered when prescribing caffeine supplementation. It remains unclear whether habituation cancels out the ergogenic benefits of caffeine on resistance exercise performance, as no evidence exists for this type of exercise. In some cases, administering placebo alone with the suggestion that it is caffeine has also been shown to enhance performance and reduce RPE. Therefore, the effectiveness of the blinding needs to be considered in future research. Caution is needed when extrapolating these conclusions to females as the vast majority of studies involved only male participants. Finally, most of the studies done in this area report small-to-moderate acute improvements in resistance exercise performance with caffeine ingestion. Therefore, future long-term intervention studies are needed to explore if such acute increases in performance with caffeine ingestion also impact long-term adaptations to resistance exercise.

Compliance with Ethical Standards

Conflict of interest

Jozo Grgic, Pavle Mikulic, Brad J. Schoenfeld, David J. Bishop and Zeljko Pedisic declare that they have no conflicts of interest relevant to the content of this review.

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