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# The Effect of Creatine on Muscle Mass Gain: A Literature Review

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**Abstract**

**Introduction and Purpose:** Creatine, a popular ergogenic aid, enhances athletic performance by influencing muscle energy reserves, protein synthesis, and growth factors. This research aims to investigate the impact of creatine on hypertrophy, comparing different types, dosages, and training methods to determine the most effective approach for promoting muscle growth.

**State of Knowledge:** Various creatine supplementation protocols exist, including loading phases and continuous low-dose strategies, with studies showing comparable effectiveness. Research on supplementation timing (pre- vs. post-exercise) is inconclusive. While creatine enhances adaptations to resistance training (RT), its impact on muscle hypertrophy is generally small and context-dependent, with the most significant benefits observed in younger males. The benefits of creatine supplementation with RT tend to diminish in older adults and females, highlighting the importance of realistic expectations regarding its role in muscle growth. Creatine monohydrate (CM) is the most thoroughly evaluated form, known for its safety, and well documented efficacy. One of the alternative forms of supplementation is creatine malate, though its effectiveness is less researched than CM.

**Conclusion:** CM consistently demonstrates efficacy in enhancing RT-induced hypertrophy without demonstrating clear supplementation protocol superiority. Modest muscle and strength gains are age- and sex-dependent, being most pronounced in younger males. Although CM remains optimal, novel forms such as malate merit further investigation. These findings highlight the importance of realistic expectations regarding creatine's role in muscle growth. Future research should consider more individual factors to optimize creatine supplementation strategies.

**Keywords:** creatine, muscle hypertrophy, resistance training, creatine monohydrate, creatine malate, creatine supplementation protocols

## Introduction.

Creatine is one of the most widely used supplements globally, favored by athletes across various disciplines due to its positive effects on enhancing physical performance.

It is a non-protein amino acid naturally found in the human body, primarily stored in skeletal muscles, and to a lesser extent in the brain, liver, kidneys, and testes. Approximately two-thirds of the body's creatine is in the form of phosphocreatine, with the remainder as free creatine. Its synthesis occurs from glycine, arginine, and methionine, mainly taking place in the liver, kidneys, and pancreas at a rate of about 1 gram per day. The human diet provides about 50% of the daily creatine requirement, while the remaining 50% is synthesized endogenously. Foods rich in creatine include meat, particularly red meat, and fish; vegetarians typically have lower muscle creatine concentrations[1]. In the body, creatine is converted into phosphocreatine, which accumulates in muscles and serves as an energy reserve.

During intense exercise, phosphocreatine releases phosphate groups that are used to reconstitute adenosine triphosphate (ATP), the primary energy carrier for muscle contraction[2]. Creatine also influences hypertrophy by increasing protein synthesis via the mTOR/P70S6K pathway, stimulating the activity of satellite cells responsible for muscle repair and growth.

Additionally, it affects the expression of insulin-like growth factor-1 (IGF-1), promoting muscle growth by attenuating the action of myostatin, which inhibits muscle hypertrophy. Another mechanism involves an inhibitory effect on TNF-α, which can have anti-inflammatory and antioxidant effects.[3][4]. The use of creatine results in increased muscle strength, accelerated post-training recovery, and enhanced physical endurance. Another important aspect of creatine use is its effect on muscle mass gain. Furthermore, creatine supplementation has shown significant positive effects on cognitive function, particularly in memory and attention among adults aged 18-60. It may also stabilize mood and alleviate symptoms of depression, enhancing emotional well-being [5][6]. This has led to attempts to use creatine in conditions such as Alzheimer's, Parkinson's, and mood disorders.

There have been numerous reports on the side effects of taking creatine, including its potential impact on alopecia, kidney failure, and liver failure;[7] however, none of these have been confirmed in studies. Another side effect of creatine use is perceived gastrointestinal discomfort, such as bloating and diarrhea[8]. It should be noted that this is a dose-dependent effect and can be minimized by using creatine with adequate water intake and splitting doses[9].

The goal of our work is to investigate the extent to which creatine affects hypertrophy, comparing its different types, dosage regimens, and training methods to identify the most optimal form for promoting muscle hypertrophy.

**Creatine supplementation protocols and muscles hypertrophy:**

Various creatine supplementation protocols have been proposed, each with distinct strategies for enhancing muscle performance. One common approach involves a loading phase, where approximately 20 grams of creatine are consumed daily for 4 to 5 days, followed by a maintenance phase with a dose of 2-5 g/day. This protocol has been shown to increase intramuscular creatine concentration by 10-40%[10]. Alternatively, creatine can be supplemented continuously without a loading phase, at a rate of about 3 g/day. A meta-analysis conducted by Scott C. Forbes and colleagues found no significant differences in the effectiveness of these two methods on muscle hypertrophy. Moreover, their results indicated that low doses of creatine (≤5 g/day) did not differ significantly from higher doses (>5 g/day) in terms of muscle mass gain[11].

Similar findings were reported by J. Chami's team, who compared muscle strength and functional gains across different creatine doses. In a double-blind study, participants were divided into three groups: high-dose creatine (0.3 g/kg/day), medium-dose creatine (0.1 g/kg/day), and placebo. Each group took the substances for 10 consecutive days. The results did not demonstrate the superiority of using higher doses of creatine on functionality and muscle strength. Both protocols have shown similar effectiveness[12]. Currently, there is no evidence suggesting that one approach is superior to the other. Nevertheless, it is noteworthy that the increase in intramuscular creatine levels in a protocol without a loading phase occurs at a more gradual pace. On the other hand, during the loading phase it is more likely for gastrointestinal side effects to occur.

Another issue under investigation is the timing of creatine intake relative to exercise. Researchers are seeking to determine when it is most beneficial to take creatine.

A 2021 randomized controlled trial examined the effect of creatine supplementation immediately before or after unilateral resistance training. The study included 10 young participants (aged 23 ± 5 years, 7 men, and 3 women) who were randomly assigned to creatine monohydrate supplementation before and after exercise versus placebo. This study lasted 8 weeks and found that taking creatine before or after exercise produced similar effects on muscle hypertrophy and strength in young adults. However, it is important to note that the study had a small sample size[13]. A meta-analysis by Scott C. Forbes and colleagues suggest that post-exercise creatine ingestion may provide greater muscle benefits than pre-exercise creatine, although this analysis included only three studies[14].

As evident from the existing research, the findings regarding the optimal timing of creatine intake remain inconclusive. Therefore, further investigation into this topic is necessary to provide clearer insights.

**The effect of creatine supplementation combined with resistance training on muscle mass gain:**

Resistance training (RT) is a form of exercise that involves the use of resistance to induce muscle contraction, leading to increased strength, muscle mass and overall fitness. This is supported by studies showing increases in skeletal muscle mass and strength in overweight and obese individuals training in this manner [15]. Resistance training affects muscle hypertrophy primarily through mechanical tension, metabolic stress, and muscle damage. These stimuli activate various biological mechanisms that promote muscle growth [16]. Creatine supplementation combined with RT can lead to even better muscle development, especially in muscle strength. This synergistic effect shows particularly noticeable effects in younger adults and men [17;18]. Below, we have presented a detailed analysis of the effects of creatine and RT on muscle hypertrophy.

Scott C. Forbes et al., in their recent 2021 meta-analysis [11] on the importance of creatine intake strategies on lean muscle mass and muscle strength in the elderly, considered recent studies [19; 20] and compared them with previous meta-analyses [21, 22]. In their study, they compared 16 randomized clinical trials ( involving a total of 509 participants). They included a group of people over the age of 50, both healthy and chronically ill. The study groups were divided into those taking creatine supplementation in combination with RT versus those taking placebo with RT. Fat-free body mass was measured using dual-energy X-ray absorptiometry (DEXA), hydrostatic weighing, air displacement plethysmography, bioelectrical impedance, or multi-site ultrasound. The conclusions were that creatine supplementation, regardless of dosing strategy, results in increased lean tissue mass and strength gains when combined with resistance training compared to placebo.

A meta-analysis conducted by E. E. P. de Santos et al. in 2021 [23] considered the effectiveness of creatine supplementation combined with resistance training on muscle strength and muscle mass in older women. This work referred to an increase in muscle mass and strength in the context of sarcopenia. A systematic literature search was conducted in nine electronic databases. Ten randomized clinical trials (RCTs) (n = 211 participants), involving mainly peri-postmenopausal women, were included in the review. Participants were randomly assigned to receive creatine or placebo during resistance training (2 to 3 times per week).

The study included both healthy women and women with osteopenia, osteoporosis, or knee osteoarthritis. A combination of resistance training and creatine supplementation was shown to increase muscle strength in older women if the training lasted at least 24 weeks. However, the researchers did not observe a significant effect on muscle mass. Additionally, they indicated that the certainty of the evidence was low (related to the limited number of subjects or the short follow-up period of 12 to 52 weeks), which may have contributed to the inaccuracy of the observed effects.

A team of researchers led by Burke conducted a comprehensive meta-analysis in 2023 [18], including 10 long-term research studies, each lasting a minimum of 6 weeks. The participants in these studies were healthy adults. Included in the analysis were studies on the long-term effects of creatine supplementation (in any form) in combination with RT, compared to RT without creatine supplementation. Local direct measurements of muscle hypertrophy were made using magnetic resonance imaging (MRI), computed tomography (CT), or ultrasound. Both univariate and multivariate analyses of the results indicated a very small favorable effect of creatine supplementation combined with RT compared to RT and placebo on changes in upper and lower body muscle thickness. However, the researchers pointed out that there is a slight advantage in favor of creatine supplementation in younger adults compared to older adults. In their conclusions, they emphasized that individuals considering creatine supplementation for regional muscle hypertrophy should take into account the practical significance of the relatively small effect size. They pointed out that further studies should additionally take into account differences in muscle remodeling for specific groups of individuals by gender or age.

One of the most recent meta-analyses in 2024 [24] on creatine supplementation protocols with or without training interventions on body composition revealed that creatine supplementation has a small but beneficial effect on parameters such as lean body mass and body fat percentage. The results of detailed analyses showed a significant increase in lean body mass when creatine supplementation was combined with aerobic and/or resistance training, regardless of the use of creatine monohydrate or its dosing strategy. In addition, creatine supplementation combined with aerobic or strength training revealed a significant reduction in body fat percentage. It is worth emphasizing that the authors found no significant differences by gender, although men reported a greater increase in fat-free mass (1.20 kg on average) compared to women (0.54 kg on average). Age, training level, and duration of the study did not affect the results. However, in their summary, the authors noted- based on the analysis of nearly 136 studies involving 3,655 participants- that creatine supplementation does not have as significant effect on body weight, its fat-free component, or body fat percentage over the long term. Nevertheless, they underlined that changes in body composition were more evident when creatine was combined with resistance training. According to them, creatine appears to increase lean body mass more in men than in women. Overall, differences in dosing protocols, training status, and age did not seem to affect the effectiveness of creatine supplementation.

Based on the presented results of meta-analyses covering an extensive number of studies, no negative consequences of creatine supplementation combined with RT on overall health have been demonstrated.

Therefore, it can be concluded that healthy individuals may experience the ergogenic benefits of creatine supplementation more prominently than its muscle hypertrophy-specific effects. Many studies have small sample sizes, short durations, and rely on indirect measures. While creatine supplementation enhances adaptations for RT, its measurable impact on muscle hypertrophy is small and context-dependent. The largest benefits are seen in younger males, with diminishing returns for older adults and females. These findings underscore the need for realistic expectations about creatine's role in muscle growth.

**Creatine monohydrate**

Currently the most commonly studied and best-tested form of creatine is monohydrate (CM) [25][26], it outsells any other available form of this supplement. The creatine content varies across different forms, thus it is worth emphasizing that CM has the highest concentration of creatine after anhydrous [26]. CM is a hydrated form of creatine that closely resembles the naturally occurring creatine synthesized in the liver, kidneys, and pancreas [33]. Creatine monohydrate safety, risk assessment and effectiveness has been evaluated by many authors. Since creatine monohydrate became popular, over a thousand studies have been conducted and the sole consistently documented side effect of creatine supplementation mentioned in the literature is weight gain [27] [28] [29]. In a Systematic Review and Meta-analysis, by Pashayee-Khamene F et al. (2024), after analyzing 143 randomized controlled trials, the researchers found that creatine supplementation led to small but significant increases in body mass and fat-free mass along with a reduction in body fat percentage These effects were more pronounced when creatine was combined with resistance training or included a maintenance dose. The study suggests that in the course of time the weight gain is possibly a combined effect of increased lean tissue mass and water retention [24]. The International Society of Sports Nutrition (ISSN) states that creatine monohydrate is currently the most potent performance-enhancing dietary supplement available in regard to enhancing high-intensity exercise capacity and increasing lean body mass during training [25]. In 1999 Kreider et. al reported greater gains in strength and muscle mass in American collegiate football players supplementing 20 or 25 g/day of creatine monohydrate with a carbohydrate/protein supplement for 12 weeks [30]. Many other studies since then have shown that creatine supplementation enhances body and/or muscle mass during training. The increase in muscle mass seems to stem from an enhanced capacity to perform high-intensity exercises, allowing athletes to train more intensely, which promotes muscle hypertrophy. In studies by Hultman et al (1996) [31] and by A.T. Askow (2022) [32] - after supplementation of creatine monohydrate an increase in muscle creatine was observed, respectively ~12% and ~24%. The samples in both trials were obtained by muscle biopsy. The difference between the outcomes is most likely caused by supplementing a higher dose of creatine monohydrate in the second study. Creatine monohydrate has been proven safe and highly effective in enhancing athletic performance and promoting muscle growth during training. CM holds a significant advantage over other forms of creatine, primarily due to its well-documented properties and established safety profile.

**Creatine malate**

Another increasingly popular, yet not as thoroughly evaluated, form of creatine is creatine malate. Its chemical structure consists of one molecule of malic acid and two or three molecules of creatine [33]. While creatine monohydrate consists of 87.9% creatine, creatine malate contains only 74.7% [26]. Malic acid itself is found in great amounts in fruits and vegetables, and humans ingest about 1.5-3g of malic acid daily with food [35]. It is also a substance commonly used as a preservative and an ingredient in cosmetic products and pharmaceutical preparations [36]. The chemical structure of creatine malate prevents the degradation of creatine to creatinine, resulting in greater efficiency of absorption and metabolism [38]. Some studies also describe that creatine malate is more absorbable in comparison to monohydrate due to its better water solubility. For the same reason, the literature describes a reduced risk of fluid retention in muscle cells with malate [38]. The effect and effectiveness of creatine malate has been researched in diverse type of sports and forms of physical activity. In studies by Tyka et. al [37] and Sterkowicz et. al [34] the researchers aimed to establish the impact of creatine malate on body composition and physical performance. In the first study [37], during a 6-week supplementation of creatine malate by sprinters and long-distance runners, a significant ergogenic effect was demonstrated among sprinters. It was reflected in an increase in anaerobic exercise and morphological indices. Meanwhile, among long-distance runners, a significant increase in the distance covered during tests was observed in the group using creatine malate, compared to the placebo group. In addition, the study also assessed hormone concentrations in venous blood after exercise. After the creatine malate loading period a significant increase in growth hormone level in blood serum was observed among sprinters. Because growth hormone enhances muscle protein production and promotes the increase of muscle mass [39][40], this finding contributes to the thesis that supplementation of creatine malate has a ergogenic effect on sprinters. An interesting course for further investigation, would be to establish the cause of different responses to supplementation of creatine malate in sprinters and long-distance runners. The study by Sterkowicz et. al [34], conducted among judo athletes, also used creatine malate as the tested supplement, however no ergogenic effect was demonstrated. This indicates that additional studies are required to understand the varying effects of creatine malate supplementation across different sports disciplines.

A number of studies can be found in the literature describing the effects of creatine on muscle mass gain, post-exercise recovery and its ergogenic effect. However, enumerating the differences between the various forms of supplemented creatine and the effects of each form on muscle mass gain remains a topic that needs to be further explored.

**Conclusion**

The findings presented herein reinforce the established role of creatine supplementation, particularly creatine monohydrate, as a valuable adjunct to resistance training for enhancing athletic performance and promoting muscle growth. The literature supports the efficacy of various creatine supplementation protocols, with no clear superiority demonstrated by either loading or non-loading strategies, or by varying dosages within the typically recommended range.

Meta-analytic evidence indicates that creatine supplementation, when combined with resistance training, consistently yields modest improvements in lean body mass and strength, although the magnitude of these effects is influenced by individual factors such as age and sex, with younger males tending to exhibit more pronounced benefits. While creatine malate presents a potentially promising alternative, further research is warranted to fully elucidate its effects on muscle hypertrophy and overall athletic performance. Ultimately, the judicious use of creatine supplementation, particularly creatine monohydrate, can be considered a safe and effective strategy for augmenting muscle adaptations and optimizing athletic outcomes, with the understanding that individual responses may vary and that realistic expectations should be maintained regarding the extent of muscle growth achievable through this intervention.

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