Creatine Supplementation for Muscle Growth

Subjects: Food Science & Technology

Contributor: ShihHao Wu

Muscle growth involves increasing muscular size, typically through strength training and protein supplementation.

ergogenic aids performance enhancement muscle growth

1. Introduction

Muscle growth involves increasing muscular size, typically through strength training and protein supplementation [1]. Dietary protein intake supports skeletal muscle remodeling after exercise by stimulating muscle protein synthesis and can optimize resistance training-mediated increases in skeletal muscle size and strength [1]. Muscle growth has been an important issue in the sports field for decades. Numerous researchers have focused on how to improve sports performance for athletics [2]. In recent years, muscle growth has also become a popular issue in clinical medicine. Sarcopenia is increasingly linked to aging and is associated with an increased likelihood of adverse outcomes, including falls, fractures, frailty, and mortality [3]. Therefore, finding ways to increase muscle strength and physical performance to prevent falling down, or even fractures, in the older population is one of the most important issues in geriatrics [4].

Numerous supplements for muscle growth have been discovered or developed since the 1980s, such as whey protein, casein, beta-hydroxy beta-methyl butyrate, omega-3 fatty acids, and creatine [5][6][7][8]. Creatine, an ergogenic compound, is an important intermediate in the metabolism of muscles, brain, and other tissues with high energy demand and fluxes [9]. It is endogenously formed from the amino acids arginine, glycine, and methionine in the kidneys and liver [10]. Exogenously, creatine is primarily consumed via meat and/or as a dietary supplement.

Creatine monohydrate supplementation can increase the phosphocreatine/creatine ratio in skeletal muscle tissue, thereby increasing the capacity for rapid adenosine triphosphate (ATP) resynthesis during repeated high-intensity exercise tasks [11][12][13][14]. The increase in lean mass following creatine supplementation has at least partly been attributed to water retention in muscle tissue [13][15]. Greater osmotic pressure following the increase in creatine content has been suggested to result in muscle cell swelling, which is considered a key stimulus for cell growth [13][14][16].

Creatine has also been a popular and effective ergogenic supplementation among athletes of all levels for decades. Despite over 50 years of research, the field of sports nutrition regarding creatine continues to grow at a rapid rate. Many studies have demonstrated that creatine supplementation, in combination with various kinds of training, is effective at augmenting training workouts and increasing muscular strength and lean body mass [14][17].

Due to the sheer volume of studies on creatine supplementation for muscle growth, some evidence of confusion and conflict exists.

2. Dosage Strategies of Creatine Supplementation

The positive effects of creatine supplementation on muscle strength, muscle mass, and sport performance seemed to only be found in healthy young adults, regardless of whether they were trained or untrained before use, and different dosage strategies were effective. In the studies of young adults, creatine supplementation without a loading dose still had a positive effect on muscle mass, sport performance, and muscle strength within two weeks [18]. Consistent with this, Antonio et al. showed increased intramuscular creatine storage, muscle accretion, and muscle performance even under lower daily dosages of creatine supplementation (i.e., 3–5 g/day) [17].

3. Exercise and Its Relationship with Creatine Supplementation

3.1. Type of Exercise That Benefits from Creatine Supplementation

Among the trials on healthy trained young subjects, resistance training, elite soccer training, canoe basic training, and plyometric training were included [15][19][20][21][22][23]. The above information revealed that all kinds of assessed exercise and training with creatine supplementation were effective for increasing muscle accretion and muscle performance. Consistent with this, Antonio et al. mentioned that a variety of athletic activities, not just those involving resistance/power, may benefit from creatine supplementation [17].

3.2. Without Exercise during the Creatine Supplementation Period

The healthy untrained subjects in the trial of del Favero et al. were instructed to refrain from any exercise training program throughout the study. However, those subjects with creatine supplementation still had increased muscle power output and muscle strength when compared to the placebo. According to the study protocol, a 12 day exercise program, including a familiarization session, 1-RM maximum dynamic strength test, and muscle power output test, was executed prior to creatine supplementation [24]. It seems that the 12 day exercise program was enough to observe muscles benefiting from creatine supplementation, including through an increase in intramuscular creatine storage and muscle growth as well as a further increase in muscle power output and muscle strength. In the trial of Backx et al., the non-immobilized leg (without training, but needing daily physical activity) and the quadricep muscle CSA did not change differently in the placebo or creatine group (p = 0.63) during immobilization. However, 1-RM of the non-immobilized leg increased during the immobilization period (p = 0.03) with no differences between the placebo and creatine groups (p = 0.90) [25]. Therefore, creatine supplementation was ineffective on muscle growth when sufficient training was lacking.

3.3. The Effect of Creatine Supplementation on Muscle Damage or Recovery

Serum creatine kinase activity reflects muscle membrane disruption, which is often elevated after exercise or resistance training. Wang et al. found that creatine kinase was obviously decreased in the creatine group when compared to the placebo control group ($p \leq 0.05$). Creatine supplementation could reduce muscle damage after training [23]. However, Kaviani et al. found that creatine kinase more obviously increased in the creatine group when compared to the placebo control group ($p < 0.05$) after whole-body resistance training. Creatine supplementation did not prevent muscle damage [18]. Thus, the results are conflicting. Jiaming et al. performed a systematic review and meta-analysis of RCTs for the effect of creatine supplementation on recovery following exercise-induced muscle damage. This revealed that creatine supplementation is effective in reducing the immediate muscle damage that happens < 24, 24, 48, 72, and 96 h post-exercise. In the current meta-analysis, the positive effects of creatine could cause a decrease in the overall CK concentration. However, due to high heterogeneity and the medium risk of bias in articles, they suggest that these results are taken into account and that the data be interpreted with caution [26]. Northeast et al. also performed a systematic review and meta-analysis of human intervention trials regarding the effect of creatine supplementation on the markers of exercise-induced muscle damage. They found that creatine supplementation does not accelerate recovery following exercise-induced muscle damage. Creatine attenuated creatine kinase activity only at 48 h post-exercise and not at any other time points. High (I^2; >75%) and significant (chi^2; $p < 0.01$) heterogeneity was identified for all outcome measures at various follow-up times [27]. Therefore, the effect of creatine supplementation on muscle damage is still controversial.

3.4. The Effect of Creatine Supplementation on Mitigating or Attenuating the Loss of Muscle Mass or Muscular Strength during Immobilization

Creatine supplementation while immobilized during casting is a research theme that has been emerging in recent years. Fransen et al. and Backx et al. found that creatine supplementation had no effects on the preservation of muscle mass or strength during casting [28][25]. However, Harmon et al. found that creatine supplementation may promote maintenance and mitigate the loss of muscle mass, muscular strength, and endurance, as well as promote healthy glucoregulation, during periods of immobilization [29]. However, different study protocols (e.g., involved muscle group, duration, and creatine dose) may have influence the observed findings [29]. Therefore, the effect of creatine supplementation on mitigating or attenuating the loss of muscle mass or muscular strength during immobilization is still controversial.

3.5. The Effect of Creatine Supplementation on Older Populations

In healthy untrained older subjects, creatine supplementation had no obvious effect on the increase in muscle strength, sport performance, or muscle hypertrophy when compared to the placebo control group. However, Candow et al. published two review articles in 2014 and 2019, mentioning that creatine may positively increase muscle mass and strength in the elderly [30][31]. However, Candow et al. found that after 12 months of training, there was no obvious increase in muscle thickness by DXA in the creatine group when compared to the placebo group [32]. Candow et al. performed another trial using pQCT for muscle density and showed that creatine supplementation may have some favorable effects on muscle density in the lower but not upper limbs [33]. In the

recent two studies of Candow et al., which measured muscle mass differently, the researchers were attempting to test a different method to find evidence that creatine promotes muscle growth. A review article by Antonio et al. mentioned that creatine supplementation in the elderly population may have a positive effect on increasing muscle mass, especially during resistance training [17]. Based on the current evidence, it is not clear whether creatine can increase muscle mass and strength in the elderly population, and more research is needed to reach a clear conclusion.

3.6. The Effect of Creatine Supplementation on Patients

Many diseases may cause muscle atrophy or muscle lesions and result in a loss of muscle strength and a decrease in quality of life. Creatine supplementation is a novel field in clinical medicine. Domingues et al. and Dover et al. revealed no obvious effect on muscular performance in the creatine group when compared to the placebo group in peripheral arterial disease and juvenile dermatomyositis, respectively. Moreover, the subjects had high compliance, with almost no side effects due to creatine supplementation. Thus, creatine appears to be safe for the human body and for all populations, with no additional adverse effects on liver and kidney function [17][34][35].

References

1. Hartono, F.A.; Martin-Arrowsmith, P.W.; Peeters, W.M.; Churchward-Venne, T.A. The Effects of Dietary Protein Supplementation on Acute Changes in Muscle Protein Synthesis and Longer-Term Changes in Muscle Mass, Strength, and Aerobic Capacity in Response to Concurrent Resistance and Endurance Exercise in Healthy Adults: A Systematic Review. Sports Med. 2022.
2. Schoenfeld, B.J.; Grgic, J.; Van Every, D.W.; Plotkin, D.L. Loading Recommendations for Muscle Strength, Hypertrophy, and Local Endurance: A Re-Examination of the Repetition Continuum. Sports 2021, 9, 32.
3. Beaudart, C.; Rizzoli, R.; Bruyère, O.; Reginster, J.Y.; Biver, E. Sarcopenia: Burden and challenges for public health. Arch. Public Health 2014, 72, 45.
4. Welch, C.; Majid, Z.; Greig, C.; Gladman, J.; Masud, T.; Jackson, T. Interventions to ameliorate reductions in muscle quantity and function in hospitalised older adults: A systematic review towards acute sarcopenia treatment. Age Ageing 2021, 50, 394–404.
5. Rossato, L.T.; Schoenfeld, B.J.; de Oliveira, E.P. Is there sufficient evidence to supplement omega-3 fatty acids to increase muscle mass and strength in young and older adults? Clin. Nutr. 2020, 39, 23–32.
6. Bear, D.E.; Langan, A.; Dimidi, E.; Wandrag, L.; Harridge, S.D.R.; Hart, N.; Connolly, B.; Whelan, K. β-Hydroxy-β-methylbutyrate and its impact on skeletal muscle mass and physical function in clinical practice: A systematic review and meta-analysis. Am. J. Clin. Nutr. 2019, 109, 1119–1132.

7. Joy, J.M.; Vogel, R.M.; Shane Broughton, K.; Kudla, U.; Kerr, N.Y.; Davison, J.M.; Wildman, R.E.C.; DiMarco, N.M. Daytime and nighttime casein supplements similarly increase muscle size and strength in response to resistance training earlier in the day: A preliminary investigation. J. Int. Soc. Sports Nutr. 2018, 15, 24.
8. Nabuco, H.C.G.; Tomeleri, C.M.; Sugihara Junior, P.; Fernandes, R.R.; Cavalcante, E.F.; Antunes, M.; Ribeiro, A.S.; Teixeira, D.C.; Silva, A.M.; Sardinha, L.B.; et al. Effects of Whey Protein Supplementation Pre- or Post-Resistance Training on Muscle Mass, Muscular Strength, and Functional Capacity in Pre-Conditioned Older Women: A Randomized Clinical Trial. Nutrients 2018, 10, 563.
9. Brosnan, J.T.; Brosnan, M.E. Creatine: Endogenous metabolite, dietary, and therapeutic supplement. Annu Rev. Nutr. 2007, 27, 241–261.
10. Wyss, M.; Kaddurah-Daouk, R. Creatine and creatinine metabolism. Physiol. Rev. 2000, 80, 1107–1213.
11. Van Loon, L.J.; Oosterlaar, A.M.; Hartgens, F.; Hesselink, M.K.; Snow, R.J.; Wagenmakers, A.J. Effects of creatine loading and prolonged creatine supplementation on body composition, fuel selection, sprint and endurance performance in humans. Clin. Sci. 2003, 104, 153–162.
12. Greenhaff, P.L.; Bodin, K.; Soderlund, K.; Hultman, E. Effect of oral creatine supplementation on skeletal muscle phosphocreatine resynthesis. Am. J. Physiol. 1994, 266, E725–E730.
13. Hultman, E.; Söderlund, K.; Timmons, J.A.; Cederblad, G.; Greenhaff, P.L. Muscle creatine loading in men. J. Appl. Physiol. 1996, 81, 232–237.
14. Kreider, R.B.; Kalman, D.S.; Antonio, J.; Ziegenfuss, T.N.; Wildman, R.; Collins, R.; Candow, D.G.; Kleiner, S.M.; Almada, A.L.; Lopez, H.L. International Society of Sports Nutrition position stand: Safety and efficacy of creatine supplementation in exercise, sport, and medicine. J. Int. Soc. Sports Nutr. 2017, 14, 18.
15. Ribeiro, A.S.; Avelar, A.; Kassiano, W.; Nunes, J.P.; Schoenfeld, B.J.; Aguiar, A.F.; Trindade, M.C.C.; Silva, A.M.; Sardinha, L.B.; Cyrino, E.S. Creatine supplementation does not influence the ratio between intracellular water and skeletal muscle mass in resistance-trained men. Int. J. Sport Nutr. Exerc. Metab. 2020, 30, 405–411.
16. Lang, F.; Busch, G.L.; Ritter, M.; Völkl, H.; Waldegger, S.; Gulbins, E.; Häussinger, D. Functional significance of cell volume regulatory mechanisms. Physiol. Rev. 1998, 78, 247–306.
17. Antonio, J.; Candow, D.G.; Forbes, S.C.; Gualano, B.; Jagim, A.R.; Kreider, R.B.; Rawson, E.S.; Smith-Ryan, A.E.; VanDusseldorp, T.A.; Willoughby, D.S.; et al. Common questions and misconceptions about creatine supplementation: What does the scientific evidence really show? J. Int. Soc. Sports Nutr. 2021, 18, 13.

18. Kaviani, M.; Abassi, A.; Chilibeck, P.D. Creatine monohydrate supplementation during eight weeks of progressive resistance training increases strength in as little as two weeks without reducing markers of muscle damage. J. Sports Med. Phys. Fit. 2019, 59, 608–612.
19. Claudino, J.G.; Mezencio, B.; Amaral, S.; Zanetti, V.; Benatti, F.; Roschel, H.; Gualano, B.; Amadio, A.C.; Serrao, J.C. Creatine monohydrate supplementation on lower-limb muscle power in Brazilian elite soccer players. J. Int. Soc. Sport Nutr. 2014, 11, 6.
20. Nunes, J.P.; Ribeiro, A.S.; Schoenfeld, B.J.; Tomeleri, C.M.; Avelar, A.; Trindade, M.C.; Nabuco, H.C.; Cavalcante, E.F.; Junior, P.S.; Fernandes, R.R.; et al. Creatine supplementation elicits greater muscle hypertrophy in upper than lower limbs and trunk in resistance-trained men. Nutr. Health 2017, 23, 223–229.
21. Yáñez-Silva, A.; Buzzachera, C.F.; Piçarro, I.D.C.; Januario, R.S.B.; Ferreira, L.H.B.; McAnulty, S.R.; Utter, A.C.; Souza-Junior, T.P. Effect of low dose, short-term creatine supplementation on muscle power output in elite youth soccer players. J. Int. Soc. Sports Nutr. 2017, 14, 5.
22. Wang, C.C.; Lin, S.C.; Hsu, S.C.; Yang, M.T.; Chan, K.H. Effects of Creatine Supplementation on Muscle Strength and Optimal Individual Post-Activation Potentiation Time of the Upper Body in Canoeists. Nutrients 2017, 9, 1169.
23. Wang, C.C.; Fang, C.C.; Lee, Y.H.; Yang, M.T.; Chan, K.H. Effects of 4-Week Creatine Supplementation Combined with Complex Training on Muscle Damage and Sport Performance. Nutrients 2018, 10, 1640.
24. Del Favero, S.; Roschel, H.; Artioli, G.; Ugrinowitsch, C.; Tricoli, V.; Costa, A.; Barroso, R.; Negrelli, A.L.; Otaduy, M.C.; da Costa Leite, C.; et al. Creatine but not betaine supplementation increases muscle phosphorylcreatine content and strength performance. Amino Acids 2012, 42, 2299–2305.
25. Backx, E.M.P.; Hangelbroek, R.; Snijders, T.; Verscheijden, M.L.; Verdijk, L.B.; de Groot, L.; van Loon, L.J.C. Creatine Loading Does Not Preserve Muscle Mass or Strength During Leg Immobilization in Healthy, Young Males: A Randomized Controlled Trial. Sports Med. 2017, 47, 1661–1671.
26. Jiaming, Y.; Rahimi, M.H. Creatine supplementation effect on recovery following exercise-induced muscle damage: A systematic review and meta-analysis of randomized controlled trials. J. Food Biochem. 2021, 45, e13916.
27. Northeast, B.; Clifford, T. The Effect of Creatine Supplementation on Markers of Exercise-Induced Muscle Damage: A Systematic Review and Meta-Analysis of Human Intervention Trials. Int. J. Sport Nutr. Exerc. Metab. 2021, 31, 276–291.
28. Fransen, J.C.; Zuhl, M.; Kerksick, C.M.; Cole, N.; Altobelli, S.; Kuethe, D.O.; Schneider, S. Impact of creatine on muscle performance and phosphagen stores after immobilization. Eur. J. Appl.

Physiol. 2015, 115, 1877–1886.

29. Harmon, K.K.; Stout, J.R.; Fukuda, D.H.; Pabian, P.S.; Rawson, E.S.; Stock, M.S. The Application of Creatine Supplementation in Medical Rehabilitation. Nutrients 2021, 13, 1825.
30. Candow, D.G.; Chilibeck, P.D.; Forbes, S.C. Creatine supplementation and aging musculoskeletal health. Endocrine 2014, 45, 354–361.
31. Candow, D.G.; Forbes, S.C.; Chilibeck, P.D.; Cornish, S.M.; Antonio, J.; Kreider, R.B. Effectiveness of Creatine Supplementation on Aging Muscle and Bone: Focus on Falls Prevention and Inflammation. J. Clin. Med. 2019, 8, 488.
32. Candow, D.G.; Chilibeck, P.D.; Gordon, J.; Vogt, E.; Landeryou, T.; Kaviani, M.; Paus-Jensen, L. Effect of 12 months of creatine supplementation and whole-body resistance training on measures of bone, muscle and strength in older males. Nutr. Health 2021, 27, 151–159.
33. Candow, D.G.; Chilibeck, P.D.; Gordon, J.J.; Kontulainen, S. Efficacy of Creatine Supplementation and Resistance Training on Area and Density of Bone and Muscle in Older Adults. Med. Sci. Sports Exerc. 2021, 53, 2388–2395.
34. De Guingand, D.L.; Palmer, K.R.; Snow, R.J.; Davies-Tuck, M.L.; Ellery, S.J. Risk of Adverse Outcomes in Females Taking Oral Creatine Monohydrate: A Systematic Review and Meta-Analysis. Nutrients 2020, 12, 1780.
35. Stares, A.; Bains, M. The Additive Effects of Creatine Supplementation and Exercise Training in an Aging Population: A Systematic Review of Randomized Controlled Trials. J. Geriatr. Phys. Ther. 2020, 43, 99–112.