Journal of
Obesity & Weight Loss Therapy

Moon and Cobbold, J Obes Weight Loss Ther 2016, 6:1
DOI: 10.4172/2165-7904.1000298

Short Communication Open Access

The Effect of Creatine Supplementation on Body Composition and Bone Health in the Elderly

Anna Moon and Christian Cobbold*

[1]School of Medicine, Cardiff University, Museum Avenue, Cardiff CF11 3AX, UK
[2]Institute for Science and the Environment, Worcester University, Worcester, UK

Abstract

Introduction: Ageing is associated with body composition changes, including decreases in muscle mass and bone content and increases in fat mass. Creatine supplementation is associated with increases in lean Tissue mass in athletes, leading to increased strength and power. There has been recent interest in if creatine supplementation may have similar effects in older individuals, to offset the changes seen in body composition and increase quality of life.

Aims: This review assesses the current literature on whether creatine supplementation in the presence or absence of resistance training improves body composition and bone health in older adults.

Results: In terms of resistance training and creatine supplementation in Combination, there is evidence for increased lean body mass following long-term investigations, above that of resistance training with placebo. Studies without resistance training mostly use acute strategies of creatine supplementation and have produced conflicting reports on lean body mass. Body fat percentage does not seem to be altered by either resistance training or creatine supplementation. The literature on creatine supplementation's effect on bone health is also inconclusive, with some reports showing significant increases in bone mineral density, whereas several others show no effect.

Conclusions: Creatine supplementation in the elderly may lead to increased lean body mass, and increased bone strength; however these results are far from conclusive. Dosing and timing supplementation protocols between studies may be responsible for the different results and future studies should concentrate on determining if acute or chronic creatine supplementation has a more beneficial effect on body composition in the elderly.

Keywords: Ageing; Creatine; Elderly; Supplementation; Resistance training; Bone health; Body composition

Introduction

In the developed world, we are seeing a rapidly expanding elderly population. Latest statistics suggest that the number of people aged over 65 is projected to rise by over 40% in the next 17 years in the United Kingdom [1]. Hence there is a greater need now than ever to understand the biochemical and anatomical changes that occur in ageing, in order to allow them a continued quality of life.

Ageing has been associated with increases in body weight and fat mass, along with decreases in muscle, protein and bone mineral content [2]. A cross-sectional study determined that the increase in fat mass percentage seen in ageing is mostly due to reduced lean mass, except for in the abdomen where the increase is due to fat deposits [3]. This increase in fat mass seen in the elderly is especially worrying as adipose tissue is an important source of pro-inflammatory mediators [4]. This state of inflammation can lead to an increase in risk for many age-related disorders such as atherosclerosis through processes such as endothelial dysfunction [5]. Furthermore, body composition changes in age often occur in the absence of actual weight changes, making investigating the differences in lean body mass and fat mass of high importance [6].

Resistance training has shown positive effects on body composition in elderly subjects [7] and if individuals are healthy enough, regular strength and cardiovascular exercises should be encouraged to maintain body health. However, a longitudinal study in healthy elderly subjects which showed decreases in lean tissues with age, reported that increased physical activity was not able to limit this loss in females at all, and only offset it slightly in males [2]. Also not all elderly subjects are able to or willing to partake in resistance exercise on a regular basis [1]. Thus an additional strategy may be advantageous in negating this lean body mass loss seen in age.

Over the past years, many studies have indicated the potential use of creatine supplementation in the elderly in order to increase strength and counteract sarcopenia [8]. Creatine is naturally synthesised within the body and is located in skeletal muscles as either free (40%) or in its phosphorylated form (PCr) [9]. It is an important molecule in energy transfer during skeletal muscle contraction, allowing for short bursts of high intensity exercise [9]. Creatine kinase maintains ADP and ATP concentrations at a near constant level for several seconds when the muscle contracts through transfer of a phosphoryl group from PCr to ADP (Figure 1) [10]. Creatine also acts through mitochondrial-myofibril shuttling, where PCr is moved from the mitochondria to the myofibrils in periods of intense exercise [11]. PCr is subsequently dephosphorylated, allowing for ATP regeneration and sustained

$$\text{Cr + ATP} \underset{}{\overset{\text{CK}}{\rightleftharpoons}} \text{PCr + ADP + H}^+$$

Figure 1: Creatine (Cr) and ATP are catalysed by creatine kinase (CK) to form PCr, which acts as an energy store when extra energy is not required.

***Corresponding author:** Christian Cobbold, Institute for Science and the Environment, Worcester University, Worcester, UK, E-mail: c.cobbold@worc.ac.uk

Received February 05, 2016; **Accepted** Februray 12, 2016; **Published** February 15, 2016

Citation: Moon A, Cobbold C (2016) The Effect of Creatine Supplementation on Body Composition and Bone Health in the Elderly. J Obes Weight Loss Ther 6: 298. doi:10.4172/2165-7904.1000298

muscle contraction, before being shuttled back to the mitochondria to be phosphorylated again [11]. Creatine supplementation is suggested to increase this free pool of creatine needed for PCr resynthesis, which may enhance energy transfer [9].

In times of requirement, for example high intensity exercise, PCr is shuttled to sites of ATP consumption, where CK catalyses the reverse reaction to replenish ATP at these sites, allowing for increased muscular contraction. PCr and ATP stores are limited however and exercise can only be sustained for approximately seconds [9] exogenous creatine may increase the efficiency of this system by providing more substrate for sustained energy provision [12].

Creatine supplementation has been reported as an effective method to increase physical performance and body mass in many studies utilising it as a sporting aid, especially those involving short, anaerobic activities [13]. Recent interest has also focused on the use of creatine in human ageing, where it has been suggested to have a role in increasing muscle strength and lean body mass, with or without associated resistance training [14]. Interestingly, creatine supplementation has also been linked to an increase in bone cell development and differentiation [15], especially important in the elderly due to the high levels of osteoporosis (OP) reported with age [1]. OP is characterised by low bone mineral density (BMD) and bone tissue deterioration that leads to an increased risk of bone fractures, often resulting in disability, reduced quality of life and mortality [16]. For many years, body weight was seen to be a clear indicator of BMD, and obesity a protective factor against OP [17]. However recent evidence suggests that obesity and OP are closely mechanistically connected, and extra weight puts elderly individuals at risk for certain fractures [18]. Furthermore, inflammation that characterises the obese state produces cytokines that may stimulate bone resorption, reducing BMD and bone strength [16]. Thus, improving body composition may be advantageous in protecting against OP. A study in patients with Duchenne muscular dystrophy reported increased bone density and reduced bone resorption markers with creatine supplementation [19], suggesting it may have a role as an aid to counteract the decline in bone mass experienced with advancing age. This could be highly advantageous as this supplementation may increase fitness and motility, allowing for a healthier and more independent lifestyle.

Aims

This review aims to investigate if there is any current evidence in the literature to indicate that creatine supplementation in the elderly population has beneficial effects in decreasing fat and prompting lean body mass in terms of muscle and bone.

The effect of creatine supplementation and resistance training on body composition

Resistance training alone is well documented for increasing lean body mass and muscular integrity [7]. Creatine supplementation combined with resistance training has been consistently shown to have a positive effect on body composition in studies on young subjects [20]. A meta-analysis on one hundred studies supplementing young subjects with creatine revealed a small but significant improvement on body composition, particularly prevalent when resistance training repetitive-bout rather than single bout ($p=0.028$) [21]. Increased muscular strength and power have also been demonstrated following creatine Supplementation and training in young men and women [13,22].

Table 1 shows a summary of studies, which have investigated body composition following a protocol of creatine supplementation and resistance training in elderly subjects between 55-90 years. There is some convincing evidence that there is an increase in body mass following a long-term protocol of creatine supplementation alongside an exercise protocol. Chrusch et al. show a significant increase in body mass, and more importantly this increase is lean body weight rather than water retention or fat [23]. Significant improvements in lean body mass have also been reported following similar protocols [24,25]. Interestingly, Tarnoplsky et al. also show significant increases in fat-free mass following only two resistance training sessions a week, a less intense exercise protocol [26]. However it should also be considered that this study supplemented participants with both creatine and CLA, although CLA has not been reported to increase lean body mass or decrease fat mass in previous literature [27]. Other studies have found contrasting results [28-31], detailing no significant differences in the creatine or placebo supplementing group beyond the effects of resistance training alone.

Interestingly, the vast majority of studies that reported increases in fat free mass did not report any difference in body fat percentage or fat mass. This suggests that the subjects are not actually losing any fat tissue, which may not change their health status in terms of risk of the inflammatory conditions associated with obesity [4]. However, these studies are mostly performed in healthy older people, thus it may be that the increased training and supplementation in an overweight or obese cohort may show different results.

It should also be mentioned that there are many differences in study protocols, with varying concentration of supplement given other a range of 70-224 days, and some investigators utilising a loading phase in addition to the general maintenance supplementation, making it difficult to directly compare the results of the protocols. However, a meta-analysis examining ten studies concluded that creatine supplementation, when combined with resistance training, significantly increased total body mass ($p = 0.04$) and fat-free mass ($p < 0.0001$) when compared with placebo [32]. Thus there is some evidence that combining resistance training with creatine supplementation can have a positive effect on body composition in the elderly.

The effect of creatine supplementation on body composition without associated resistance exercise programmes

As stated above, a previous meta-analysis has shown that resistance training and creatine supplementation may lead to an increase in fat-free mass [32], although this may be independent of reductions in fat tissue itself. However, it has not been examined as to whether this is true without resistance training. Table 2 shows a summary of body composition results from protocols without any associated exercise. Most of these studies only used an acute creatine supplementation protocol, unlike those with resistance training, which were more long-term studies. Gotshalk et al. [33,34] showed significant increases in body mass in both males and females following a creatine supplementation protocol, which is attributed to increases in fat free mass. Rawson and Clarkson also show a small but significant increase in fat-free mass in male subjects [35], however this effect was not seen in an earlier longer-term study [36]. Multiple other studies have reported no effect on body composition with creatine supplementation [37,38]. The differences in supplementation protocols used for these studies may contribute to the varying results, as it may be that short-term dosing has different effects than long-term studies. Only one recent study on elderly women by Lobo et al. used a long-term strategy for assessing any potential improvements [39]. They reported no differences between creatine and placebo supplementation. However they also used a very low dose, much lower than those used in conjunction with resistance training

Citation: Moon A, Cobbold C (2016) The Effect of Creatine Supplementation on Body Composition and Bone Health in the Elderly. J Obes Weight Loss Ther 6: 298. doi:10.4172/2165-7904.1000298

Study'	Supplementation	Training ssions/wk	Body Mass	Fat Mass	Fat Free Mass	% Body Fat
Aguiar et al. 2013	5 g/d for 84 days	3	NS	-	Muscle Mass SD + 3.7%, P<0.01	NS
Bermon et al. [29]	5 g/d for 98 days	3	NS	NS	NS	NS
Bermon et al. [38]	LP = 7 g/day for 14 days on training days MP = 5 g/day for 98 days on training days	3	-	-	NS	NS
Brose et al. [24]	5 g/d for 98 days	3	SD + 1.2 kg (P<0.05)	NS	SD + 1.3 kg (P <0.05)	NS
Candow et al. [25]	0.1 $g.kg^{-1}$ on training days only for 70 Days (Average Cr/d = 8.6 g/d)	3	SD + 1 kg (P<0.05)	-	SD + 1.5 kg (P<0.05)	-
Candow et al. [43]	0.1 $g.kg^{-1}$ on training days only for 224 days	3	-	NS	SD + 3 kg (P<0.025)	-
Chilibeck et al. [43]	LP = 0.3 $g.kg^{-1}$ for 5 days MP = 0.07 $g.kg^{-1}$ for 79 days (Average Cr/d: LP = 26.4 g/d MP = 6.16 g/d)	3	NS	-	NS	-
Chrusch et al. [23]	(LP = 0.3 $g.kg^{-1}$ body mass for 5 days MP= 0.07 $g.kg^{-1}$ body mass for 79 days Average Cr/d: LP = 26.4 g/d MP = 6.16 g/d)	3	SD + 3 kg (P <0.05)	NS	SD + 3.3 kg (P <0.05)	NS
Eijinde et al. 1985	5 g/d for 185 days	2-3	NS	NS	NS	NS
Gualano et al. 2014	LP: 20 g/day for 5 days MP: 5 g/day for 161 days	2	NS	NS	SD +1.31% (P<0.05)	NS
Tarnopolsky et al. 2007	5 g/day for 168 days	2	-	-	SD + 1.2 kg (P<0.05)	NS

Table 1: Summary table of key studies investigating the effect of creatine supplementation on body composition in elderly subjects with combined resistance training programmes. Cr: Creatine. LP: Loading Phase. MP: Maintenance Phase. G/d: grams per day. SD: significant difference. NS: No significant difference. -: Not measured. Values given are improvements made after creatine supplemented training compared with placebo.

Study	Supplementation	Body Mass	Fat Mass	Fat Free Mass	% Body Fat
Gotshalk et al. [34]	0.3 $g.kg^{-1}$ body mass for 7 days	SD + 1.86 kg (P<0.05)	-	SD +2.22 kg (P<0.05)	NS
Gotshalk et al. [33]	0.3 $g.kg^{-1}$ body mass for 7 days	SD + 0.49 kg (P<0.05)	-	SD +0.52 kg (P<0.05)	NS
Lobo et al. [39]	1 g/d for 365 days	NS	NS	NS	NS
Rawson and Clarkson, [35]	20 g of Cr for 5 days	-	-	SD +0.5 kg	NS
Rawson et al. [36]	LP: 20 g of Cr for 10 days MP: 4 g for 20 days	NS	NS	NS	NS
Stout et al. [37]	LP: 20 g/day for 7 days MP: 10 g/day for 7 days	NS	NS	NS	NS
Wiroth et al. [38]	15 g/day for 5 days	NS	NS	NS	NS

Table 2: Summary table of key studies investigating the effect of creatine supplementation on body composition in elderly subjects without associated resistance training. Cr: Creatine. LP: Loading Phase. MP: Maintenance Phase. G/d: grams per day. SD: significant difference. NS: No significant difference. -: Not measured. Values given are improvements made after creatine supplemented training compared with placebo.

(Table 1), suggesting that the creatine supplement may have been too low to see any significant effects. Long-term studies with a higher dose of creatine without any training are needed to make any strong conclusions as to the efficacy of creatine without resistance training to improve body composition. Also, the mechanisms as to how acute creatine supplementation has implications on body mass should be further investigated in terms of how it differs from chronic or long-term supplementation.

The effect of creatine supplementation on bone mass

OP is a common and deliberating condition associated with the elderly [3]. The causes are complex and range from genetics, hormone changes and diet alterations that are associated with advancing age [1]. Resistance training is often recommended in order to build bone mineral content and offset the bone damage and osteocyte loss seen with OP [40]. There have been some promising results [41], however recent interest in creatine supplementation have concentrated on whether the supplement can further these results. In an initial study by Chilibeck et al. following a 12 week protocol of training and supplementation (Table 3), a significant increase in BMD in the arm (3.2%) was observed, correlating with an increased, but insignificant, lean muscle at the site [30]. However this promising early study was not replicated by further experiments [26,42] who reported no differences in bone health following similar protocols. Chilibeck et al. published a follow up long-term study and showed that creatine supplementation combined with resistance training showed a decreased bone mineral loss in the femur compared to placebo [43]. This may suggest that a long-term supplementation protocol is needed to see differences in bone health, alongside resistance training.

Conclusions

Creatine supplementation has been put forward as a candidate to improve body composition in the elderly due to being a fairly safe supplement, with very few adverse effects being reported [44]. Some studies have noted an increase in gastrointestinal complaints, but this may also be due to the uptake of resistance training in combination with creatine [44]. There are very few reports of kidney problems following ingestion of creatine, important in terms of the age of the subjects addressed in these studies.

In combination with resistance training, there is some reasonably strong evidence that creatine supplementation can increase lean mass and improve muscular strength [32]. Creatine is thought to illicit this

Study	Supplementation	Training sessions/wk	Bone health parameters
Chilibeck et al. [30]	LP = 0.3 g.kg^{-1} body mass for 5 days MP = 0.07 g.kg^{-1} body mass for 79 days Average: LP = 26.4 g/day MP = 6.16 g/day	3	Increased arm BMD (3.2%, p <0.01)
Chilibeck et al. [43]	0.1 g.kg^{-1} body mass for 365 days	3	Decreased femoral neck BMD loss (CR = -1.9 vs. Placebo = -3.9%, P < 0.05) Increased femoral shaft subperiosteal width (Cr = +0.25 cm vs. placebo = +0.22 cm, P <0.05)
Gualano et al. [42]	LP: 20 g/day for 5 days MP: 5 g/day for 161 days	2	NS
Lobo et al. [39]	1 g/d for 365 days	0	NS
Tarnopolsky et al. [8]	5 g/day for 168 days	2	NS

Table 3: Summary table of key studies investigating the effect of creatine supplementation on bone health parameters in elderly subjects. Cr: Creatine. LP: Loading Phase. MP: Maintenance Phase. G/d: grams per day. SD: significant difference. NS: No significant difference. -: Not measured. BMD: Bone Mineral Density. Values given are improvements made after creatine supplemented training compared with placebo

effect through several mechanisms, for example through activation of myogenic transcription factors, such as Myo-D, myogenin and MRF-4 [45,46]. This may also lead to enhancement of satellite cell activation which progress along the myogenic lineage to produce activated myoblasts, eventually fusing to become a myofibril [47]; similar to increases in satellite cells seen during resistance training. This has particular relevance in the elderly population as satellite cell populations are known to decline with advancing age [48]. This may lead to the suggestion that activation of myogenic transcription factors by satellite cell recruitment are part of the mechanism that resistance training and creatine supplementation activate to increase muscle mass and strength.

Another important question to be addressed is whether creatine supplementation can improve body composition without any resistance training, as a large proportion of the elderly population are unlikely to partake in regular strength training. Only one group has shown significant gains in lean body mass in both male and female older subjects [33,34] while others report only small or insignificant changes. It could be suggested that the differences seen in Gotshalk et al's study can be contributed to water retention as they utilise an acute short-term protocol [49]. Creatine is a powerful osmolyte, inducing water loading in muscle, which may account for the increase seen in body mass [49]. However this in itself may be useful, as it may lead to increased muscle mass itself through protein synthesis or a decrease in muscle atrophy [33].

In terms of bone, studies on rats, both healthy and ovariectomised [50] have shown increases in bone mineral density with creatine supplementation. Translating these results to humans led to some initial evidence of long-term creatine supplementation could offset bone loss in the elderly with osteopenia and osteoporosis in males [30]. However further investigations did not fully support these observations, particularly in studies on postmenopausal women [39]. There may be an explanation for this; exercise appears to be less effective at increasing bone mass in elderly women compared to younger subjects [51], an effect which may be replicated with creatine supplementation. Also it may be the case that a more intensive exercise plan is required to increase bone mass, particualry if the increase is due to an enhanced load on the bone at muscle attachment sites [30].

There are also several limitations in these studies. Most experimental studies do not measure muscle creatine or PCr levels in order to see if the supplement has also resulted in increased creatine. This is relevant as Syrootuik and Bell have suggested that subjects may be responders and non-responders to creatine, mainly due to skeletal muscle fibre type [52], which may partly explain the differences in results between subjects. It may be suggested that determining a subject's muscle fibre physiological profile, potentially through genetic profiling, may be advantageous in order to compare groups within a study. Furthermore, several studies suffer from low sample sizes and heterogeneous populations in terms of exact age or health status. These factors all could have confounded some of the conclusions each study came to. In conclusion, ageing is associated with increasing body fat and decreases in lean body mass [2]. This can contribute too many disorders associated with ageing, such as sarcopenia, osteoporosis and inflammatory conditions such as atherosclerosis, thus it is of high interest to design strategies to improve body composition [1]. Resistance training is a well-documented intervention for sarcopenia and current knowledge seems to suggest that creatine supplementation alongside a structured resistance training plan may enhance the effects seen on reducing fat and increasing lean body mass in terms of muscle and bone. This increase in muscular strength could increase functional performance, allowing them an advanced ability to deal with daily tasks such as walking, which itself could contribute towards general fitness and health in the elderly.

References

1. Later Life in the United Kingdom - December 2015: Age UK; 2015.
2. Genton L, Karsegard VL, Chevalley T, Kossovsky MP, Darmon P, et al. (2011) Body composition changes over 9 years in healthy elderly subjects and impact of physical activity. Clin Nutr 30: 436-442.
3. Atlantis E, Martin SA, Haren MT, Taylor AW, Wittert GA; Florey Adelaide Male Aging Study (2008) Lifestyle factors associated with age-related differences in body composition: the Florey Adelaide Male Aging Study. Am J Clin Nutr 88: 95-104.
4. Fantuzzi G (2005) Adipose tissue, adipokines, and inflammation. J Allergy Clin Immunol 115: 911-919.
5. Singh T, Newman AB (2011) Inflammatory markers in population studies of aging. Ageing Res Rev 10: 319-329.
6. St-Onge MP, Gallagher D (2010) Body composition changes with aging: the cause or the result of alterations in metabolic rate and macronutrient oxidation? Nutrition 26: 152-155.
7. Candow DG (2011) Sarcopenia: current theories and the potential beneficial effect of creatine application strategies. Biogerontology 12: 273-281.
8. Kley RA, Vorgerd M, Tarnopolsky MA (2007) Creatine for treating muscle disorders. Cochrane DatabaseSyst Rev 6: CD004760.
9. Wyss M, Kaddurah-Daouk R (2000) Creatine and creatinine metabolism. Physiol Rev 80: 1107-1213.

10. Kushmerick MJ (1998) Energy balance in muscle activity: simulations of ATPase coupled to oxidative phosphorylation and to creatine kinase. Comp Biochem Physiol B Biochem Mol Biol 120: 109-123.

11. Saks VA, Ventura-Clapier R, Aliev MK (1996) Metabolic control and metabolic capacity: two aspects of creatine kinase functioning in the cells. Biochim Biophys Acta 1274: 81-88.

12. Sweeney HL (1994) The importance of the creatine kinase reaction: the concept of metabolic capacitance. Med Sci Sports Exerc 26: 30-36.

13. Greenhaff PL, Bodin K, Soderlund K, Hultman E (1994) Effect of oral creatine supplementation on skeletal muscle phosphocreatine resynthesis. Am J Physiol 266: E725-730.

14. Moon A, Heywood L, Rutherford S, Cobbold C (2013) Creatine supplementation: can it improve quality of life in the elderly without associated resistance training? Curr Aging Sci 6: 251-257.

15. Gerber I, ap Gwynn I, Alini M, Wallimann T (2005) Stimulatory effects of creatine on metabolic activity, differentiation and mineralization of primary osteoblast-like cells in monolayer and micromass cell cultures. Eur Cell Mater 10: 8-22.

16. Gonnelli S, Caffarelli C, Nuti R (2014) Obesity and fracture risk. Clin Cases Miner Bone Metab 11: 9-14.

17. De Laet C, Kanis JA, Oden A, Johanson H, Johnell O, et al. (2005) Body mass index as a predictor of fracture risk: a meta-analysis. Osteoporosis international: a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 16: 1330-8.

18. Beck TJ, Petit MA, Wu G, LeBoff MS, Cauley JA, et al. (2009) Does obesity really make the femur stronger? BMD, geometry, and fracture incidence in the women's health initiative-observational study. Journal of bone and mineral research: the official journal of the American Society for Bone and Mineral Research 24: 1369-79.

19. Louis M, Lebacq J, Poortmans JR, Belpaire-Dethiou MC, Devogelaer JP, et al. (2003) Beneficial effects of creatine supplementation in dystrophic patients. Muscle Nerve 27: 604-610.

20. Bemben MG, Lamont HS (2005) Creatine supplementation and exercise performance: recent findings. Sports Med 35: 107-125.

21. Branch JD (2003) Effect of creatine supplementation on body composition and performance: a meta-analysis. Int J Sport Nutr Exerc Metab 13: 198-226.

22. Kreider RB (2003) Effects of creatine supplementation on performance and training adaptations. Mol Cell Biochem 244: 89-94.

23. Chrusch MJ, Chilibeck PD, Chad KE, Davison KS, Burke DG (2001) Creatine supplementation combined with resistance training in older men. Med Sci Sports Exerc 33: 2111-2117.

24. Brose A, Parise G, Tarnopolsky MA (2003) Creatine supplementation enhances isometric strength and body composition improvements following strength exercise training in older adults. J Gerontol A Biol Sci Med Sci 58: 11-19.

25. Candow DG, Little JP, Chilibeck PD, Abeysekara S, Zello GA, et al. (2008) Low-dose creatine combined with protein during resistance training in older men. Med Sci Sports Exerc 40: 1645-1652.

26. Tarnopolsky M, Zimmer A, Paikin J, Safdar A, Aboud A, et al. (2007) Creatine monohydrate and conjugated linoleic acid improve strength and body composition following resistance exercise in older adults. PLoS One 2: e991.

27. Kreider RB, Ferreira MP, Greenwood M, Wilson M, Almada AL (2002) Effects of conjugated linoleic acid supplementation during resistance training on body composition, bone density, strength, and selected hematological markers. J Strength Cond Res 16: 325-334.

28. Bemben MG, Witten MS, Carter JM, Eliot KA, Knehans AW, et al. (2010) The effects of supplementation with creatine and protein on muscle strength following a traditional resistance training program in middle-aged and older men. J Nutr Health Aging 14: 155-159.

29. Bermon S, Venembre P, Sachet C, Valour S, Dolisi C (1998) Effects of creatine monohydrate ingestion in sedentary and weight-trained older adults. Acta Physiol Scand 164: 147-155.

30. Chilibeck PD, Chrusch MJ, Chad KE, Shawn Davison K, Burke DG (2005) Creatine monohydrate and resistance training increase bone mineral content and density in older men. J Nutr Health Aging 9: 352-353.

31. Eijnde BO, Van Leemputte M, Goris M, Labarque V, Taes Y, et al. (2003) Effects of creatine supplementation and exercise training on fitness in men 55-75 yr old. J Appl Physiol (1985) 95: 818-828.

32. Devries MC, Phillips SM (2014) Creatine supplementation during resistance training in older adults-a meta-analysis. Med Sci Sports Exerc 46: 1194-1203.

33. Gotshalk LA, Kraemer WJ, Mendonca MA, Vingren JL, Kenny AM, et al. (2008) Creatine supplementation improves muscular performance in older women. Eur J Appl Physiol 102: 223-231.

34. Gotshalk LA, Volek JS, Staron RS, Denegar CR, Hagerman FC, et al. (2002) Creatine supplementation improves muscular performance in older men. Med Sci Sports Exerc 34: 537-543.

35. Rawson ES, Clarkson PM (2000) Acute creatine supplementation in older men. Int J Sports Med 21: 71-75.

36. Rawson ES, Wehnert ML, Clarkson PM (1999) Effects of 30 days of creatine ingestion in older men. Eur J Appl Physiol Occup Physiol 80: 139-144.

37. Stout JR, Sue Graves B, Cramer JT, Goldstein ER, Costa PB, et al. (2007) Effects of creatine supplementation on the onset of neuromuscular fatigue threshold and muscle strength in elderly men and women (64-86 years). J Nutr Health Aging 11: 459-464.

38. Wiroth JB, Bermon S, Andreï S, Dalloz E, Hébuterne X, et al. (2001) Effects of oral creatine supplementation on maximal pedalling performance in older adults. Eur J Appl Physiol 84: 533-539.

39. Lobo DM, Tritto AC, da Silva LR, de Oliveira PB, Benatti FB, et al. (2015) Effects of long-term low-dose dietary creatine supplementation in older women. Exp Gerontol 70: 97-104.

40. Layne JE, Nelson ME (1999) The effects of progressive resistance training on bone density: a review. Med Sci Sports Exerc 31: 25-30.

41. Martyn-St James M, Carroll S. (2006) High-intensity resistance training and postmenopausal bone loss: a meta-analysis. Osteoporosis international: a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA 17: 1225-40.

42. Gualano B, Macedo AR, Alves CR, Roschel H, Benatti FB, (2014) et al. Creatine supplementation and resistance training in vulnerable older women: a randomized double-blind placebo- controlled clinical trial. Exp Gerontol 53: 7-15.

43. Chilibeck PD, Candow DG, Landeryou T, Kaviani M, Paus-Jenssen L (2015) Effects of Creatine and Resistance Training on Bone Health in Postmenopausal Women. Med Sci Sports Exerc 47: 1587-1595.

44. Poortmans JR, Francaux M (2000) Adverse effects of creatine supplementation: fact or fiction? Sports Med 30: 155-170.

45. Hespel P, Op't Eijnde B, Van Leemputte M, Ursø B, Greenhaff PL, et al. (2001) Oral creatine supplementation facilitates the rehabilitation of disuse atrophy and alters the expression of muscle myogenic factors in humans. J Physiol 536: 625-633.

46. Willoughby DS, Rosene JM (2003) Effects of oral creatine and resistance training on myogenic regulatory factor expression. Med Sci Sports Exerc 35: 923-929.

47. Olsen S, Aagaard P, Kadi F, Tufekovic G, Verney J, et al. (2006) Creatine supplementation augments the increase in satellite cell and myonuclei number in human skeletal muscle induced by strength training. J Physiol 573: 525-34.

48. Gibson MC, Schultz E (1983) Age-related differences in absolute numbers of skeletal muscle satellite cells. Muscle Nerve 6: 574-580.

49. Mesa JL, Ruiz JR, González-Gross MM, Gutiérrez Sáinz A, Castillo Garzón MJ (2002) Oral creatine supplementation and skeletal muscle metabolism in physical exercise. Sports Med 32: 903-944.

50. Antolic A, Roy BD, Tarnopolsky MA, Zernicke RF, Wohl GR, et al. (2007) Creatine monohydrate increases bone mineral density in young Sprague-Dawley rats. Med Sci Sports Exerc 39: 816-820.

51. Nikander R, Sievänen H, Heinonen A, Daly RM, Uusi-Rasi K, et al. (2010) Targeted exercise against osteoporosis: A systematic review and meta-analysis for optimising bone strength throughout life. BMC Med 8: 47.

52. Syrotuik DG, Bell GJ (2004) Acute creatine monohydrate supplementation: a descriptive physiological profile of responders vs. nonresponders. J Strength Cond Res 18: 610-617.