

Published in final edited form as:

Curr Opin Clin Nutr Metab Care. 2009 November ; 12(6): 623–627. doi:10.1097/MCO.0b013e328331de63.

Can the use of creatine supplementation attenuate muscle loss in cachexia and wasting?

Giorgos K. Sakkas^{1,2}, Morris Schambelan^{3,4}, and Kathleen Mulligan^{3,4}

¹Department of Medicine, University of Thessaly, Greece

²Center for Research and Technology, Thessaly, Greece

³Department of Medicine, University of California, San Francisco, CA, USA

⁴Division of Endocrinology, San Francisco General Hospital, San Francisco, CA, USA

Abstract

Purpose of review—Weight loss and low BMI due to an underlying illness have been associated with increased mortality, reduced functional capacity, and diminished quality of life. There is a need for safe, long-term approaches to maintain body weight in patients with cachexia or wasting. The purpose of this review is to highlight the scientific and clinical evidence derived from the recent literature investigating the rationale for and potential medical use of creatine supplementation in patients with cachexia or wasting.

Recent findings—Some studies have demonstrated that supplementation with creatine can increase creatine reserves in skeletal muscle and increase muscle mass and performance in various disease states that affect muscle size and function. The mechanisms underlying these effects are not clear. It has been suggested that creatine supplementation may increase intramuscular phosphocreatine stores and promote more rapid recovery of adenosine triphosphate levels following exercise, thus allowing users to exercise for longer periods or at higher intensity levels. Other hypothesized mechanisms include attenuation of proinflammatory cytokines, stimulation of satellite cell proliferation, and up-regulation of genes that promote protein synthesis and cell repair.

Summary—Creatine is a generally safe, low cost, over-the-counter nutritional supplement that shows potential in improving lean body mass and functionality in patients with wasting diseases. However, placebo-controlled studies have shown variable effects, with improvements in some and not in others. Additional studies with longer follow-up are required to identify the populations that might benefit most from creatine supplementation.

Keywords

lean body mass; muscle mass; energy metabolism; creatine

Corresponding Author: Kathleen Mulligan, PhD, Department of Medicine, University of California, San Francisco, San Francisco General Hospital, 1001 Potrero Avenue, Bldg 30, Room 3501-K, San Francisco, CA 94110, USA, kathleen.mulligan@ucsf.edu, Phone: (415) 206-5882.

Disclosure: The authors have declared that there is no conflict of interest.

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Introduction

According to a recent consensus conference, cachexia “is a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass” [1]. The reductions of skeletal muscle mass and fat mass occur in the context of severe weight loss [2**]. Weight loss and/or abnormally low BMI have been associated with increased mortality, reduced functional capacity and diminished quality of life [3]. More importantly, apart from the overall reduction in body mass, skeletal muscle atrophy, occurring as a result of either increased protein degradation or diminished protein synthesis, not only affects overall metabolism and mobility but, if untreated, can lead to death due to respiratory and cardiac muscle failure [4]. Treatments that reverse or forestall muscle loss could provide a potential target for the therapeutic approach to this syndrome.

A variety of non-pharmacological approaches to the treatment of muscle wasting have been investigated. Supplementation with creatine has been shown to improve muscle strength and delay fatigue, increase fat-free mass and enhance mitochondrial energy metabolism [5**]. The aim this review is to highlight the scientific and clinical evidence derived from the recent literature investigating the rationale and potential therapeutic role of creatine supplementation in patients with cachexia or wasting.

Skeletal muscle loss in cachexia

Skeletal muscle protein breakdown occurs when the balance between protein synthesis and degradation is impaired. The preponderance of evidence supports the notion that muscle mass in wasting diseases is regulated primarily by protein synthesis, while changes in the rate of protein degradation are likely secondary [6]. However, studies using experimental models of cachexia suggest that both synthesis and degradation processes are involved simultaneously in cachectic conditions [2**]. Independent of the metabolic pathway, the resultant loss of skeletal muscle mass is related to diminished quality of life, severe fatigue, and reduced physical and functional capacity, factors that may reduce life expectancy [2**].

Therapeutic use of creatine supplementation in cachexia

Creatine is a nutritional supplement that can be purchased over the counter and has been shown to increase energy availability during intense exercise, improve recovery after muscle fatigue, and increase muscle strength and size as well as total body weight and lean body mass [7,8]. Daily oral supplementation of creatine can substantially increase the creatine reserves of human skeletal muscles [9].

Furthermore, there is also evidence that creatine supplementation has a therapeutic role in various disease states that affect muscle size and functionality through the enhancement of gene expression involved in hypertrophy [10] or the attenuation of the degenerative phase in certain myopathies [11]. Many neuromuscular and neurometabolic disorders are characterized by low intramuscular phosphocreatine levels, which contribute to increased fatigability and low functionality, factors well known to increase mortality [12]. Since these disorders share quite common pathways of cellular dysfunction, it has been hypothesized that the supplementation of creatine may favorably influence functionality and may improve quality of life. Studies in patients with various catabolic illnesses as well as in animal models have shown evidence of enhanced mitochondrial function and improved exercise performance following creatine supplementation [12]. However these findings cannot be generalized to all catabolic diseases. For example, in HIV-infected patients, creatine supplementation failed to enhance the benefits derived from three months of resistance exercise training [8*].

Discrepancies in the literature are also seen in studies with healthy volunteers. Studies of short-term (5-30 days) and chronic use (up to 12 months) of creatine supplementation have shown increases in total body weight [13,14], muscle size [15], muscle strength and power output [16,17] as well as intramuscular PCr levels (assessed by both ^{31}P -MRS [18] and biopsy [19]), while other studies have failed to demonstrate positive effects on these same parameters [20-23]. The purported beneficial effect of creatine supplementation in patients with chronic diseases has been similarly challenged, with some studies showing positive effects [24-30] and others showing no benefit [31-35] (Table 1). It is not clear yet whether exercise training is needed in order to optimize the effect of creatine. However, preliminary data suggested that subjects who received both creatine and exercise training had amplified benefits compared to those who received exercise or creatine alone [37].

Creatine effect on muscle growth

Recent evidence sheds some light on the purported growth-promoting effects of creatine in skeletal muscle. Olsen et al. [37] reported that in healthy humans creatine supplementation in combination with strength training amplified the increase in satellite cell number and myonuclei concentration in skeletal muscle fibers, thus facilitating muscle growth and hypertrophy [37]. Creatine has also been reported to enhance expression of myogenin and other myogenic regulatory factors that regulate myosin heavy chain expression, affecting thus the contractile protein content (actin and myosin) [38]. It has been speculated that the potential growth-promoting effect that creatine exerts on skeletal muscle could be very useful in situations in which anabolic activity is suppressed, such as wasting diseases [39]. Further evidence of a growth-promoting effect of creatine supplementation was provided in a recent human study in which creatine supplementation significantly upregulated the mRNA content of genes and proteins involved in protein and glycogen synthesis regulation, satellite cell proliferation and differentiation, DNA replication and repair, RNA transcription control, and cell survival; and reduced whole-body protein breakdown and leucine oxidation in humans [10]. The mechanism of action is still not clear. However, it has been suggested that water retention in muscle fibers caused by the osmotic potential of high intracellular creatine abundance [40] may be a major anabolic proliferative signal.

Creatine supplementation in patients with muscle wasting and disuse

In muscle wasting, the preservation of the existing skeletal muscle mass is as important as attempts to return muscle mass to normal levels. Studies in rodents with steroid-induced myopathy have shown that creatine supplementation can reduce muscle loss, stabilize body weight, and preserve maximum oxygen consumption levels within normal range, thus exerting prophylactic effects compared to the animals with no creatine supplementation [41]. In research using disuse atrophy models, creatine supplementation for short periods attenuated skeletal muscle loss and preserved strength in the immobilized limbs [36*]. Creatine is taken up by both fast- and slow-twitch fibers, but fast-twitch fibers have a greater capacity for creatine storage than slow-twitch [42]. This difference could be very important for preservation of muscle fiber size since, in cachectic conditions, the fast-twitch fibers are lost more rapidly than slow twitch fibers, possibly due to an increase in protein oxidation and degradation [43] coupled with hypokinesia. So far, human studies have not yet demonstrated dramatic increases in skeletal muscle mass as a result of creatine supplementation, but no studies that have been conducted in cachectic patients were designed to directly address such a question. Still, Kley et al. [11] performed an excellent meta-analysis with the primary aim to determine the efficacy of creatine supplementation in various types of muscle disorders. The authors concluded from twelve trials with 266 patients that creatine supplementation in patients with muscular dystrophies significantly increased maximum voluntary contraction and lean body mass during creatine treatment

compared to placebo [11]. However, they observed no improvements in patients with metabolic myopathies. Creatine supplementation showed only a moderate improvement in ATP consumption and PCr levels in patients with metabolic myopathies, possibly due to a defect in muscle creatine uptake [5**].

Potential Ancillary Effect of Creatine Supplementation

It has been suggested by some investigators that cachexia is a condition of excess cytokine production that causes muscle loss, insulin resistance and oxidative stress [44]. Recent evidence suggests that creatine supplementation may attenuate the increase in plasma levels of the proinflammatory cytokines [45] and, in conjunction with aerobic exercise, while producing a greater improvement of glucose tolerance in humans [46*] and a protective effect on preventing immobilization induced decrease in muscle GLUT4 protein content, compared with aerobic exercise alone [47]. It has also been suggested that creatine supplementation could work as an appetite stimulant, since from studies in animal models, it has been found that creatine concentration in the brain plays a role in food intake regulation and body weight [48]. The mechanisms behind the observed anti-inflammatory and/or glucose sensitizing effect of creatine are not understood. However, further research is needed to clarify whether these improvements are due to a systemic or local effect of creatine, on leukocytes and skeletal muscles.

Safety of creatine supplementation

When creatine is used according to the international guidelines for dosage and duration of supplementation [49] it is generally considered to be safe. Early reports of impairment of renal function were prompted by reports of elevated creatine kinase levels in the blood following a period of high dosage supplementation [50]. Similarly, supplementation with higher-than-recommended doses of creatine was associated with worsening exercise intolerance in patients with McArdle disease [34]. Based on a comprehensive review of the literature, it does not appear that creatine supplementation impairs renal function if it is taken according to recommended dosage regimens. However, long-term safety data on creatine supplementation are still not available [42]. Certainly, creatine supplementation should not be considered in patients with renal disease, and creatine kinase levels should be monitored during supplementation.

Conclusion

Creatine supplementation has been suggested as a prophylactic or therapeutic agent in wasting diseases that affect muscle size and function. However, placebo-controlled studies have shown variable effects, with improvements in some and none in others. Additional studies with longer follow-up are required to identify the populations that might benefit most from creatine supplementation.

Acknowledgments

Funding: This work was supported in part with support from the National Institutes of Health (AT00491, DK45833, DK54615, RR-00083).

The authors have declared that there is no conflict of interest. We acknowledge Dr. Christina Karatzaferi for critically reviewing the manuscript. This work was supported in part with support from the National Institutes of Health (AT00491, DK45833, DK54615, RR-00083).

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* of special interest, ** of outstanding interest.

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Table 1

Summary of randomized clinical trials investigating the effect of creatine supplementation in conditions that are associated with cachexia, muscle wasting, or functional impairment.

Author, year [reference number]	Population (N)	Study Design	Duration of Supplementation	Effects of Creatine
Gordon, 1995 [26]	Chronic heart failure (N=17)	RCT	7 days	↑Strength ↑Endurance
Tarnopolsky, 1997 [25]	Mitochondrial cytopathy (N=7)	RCT, crossover	21 days	↑MVC, ↑Exercise output, ↓Fatigue
Vorgerd, 2000 [30]	McArdle disease (N=9)	RCT, crossover	5 wks	↑ Exercise tolerance ↑ PCr depletion during exercise
Walter, 2000 [28]	Muscular dystrophies (N=36)	RCT, crossover	8 wks	↑MVC, ↑ Physical activity
Hespel, 2001 [15]	Disuse atrophy model (N=22)	RCT	10 wks + rehab exercise	↑Muscle CSA, ↑Exercise output, ↓Fatigue
Walter, 2002 [33]	Myotonic dystrophy (N=34)	RCT	8 wks	↔ Muscle strength
Vorgerd, 2002 [34]	McArdle disease (N=19)	RCT, crossover	5 wks	↓ Exercise tolerance with high-dose creatine
Tarnopolsky, 2004 [31]	Myotonic muscular dystrophy type 1 (N=34)	RCT, crossover	36 wks	↔ LBM, ↔MVC, ↔Physical activity
Tarnopolsky, 2004 [27]	Children with Duchenne muscular dystrophy (N=30)	RCT, crossover	4 mos	↑ Grip strength↑ LBM
Tarnopolsky, 2007 [29]	Adults >65 years (N=39)	RCT	6 mos + linoleic acid & resistance exercise	↑ LBM↑ Muscle endurance↔ Strength, ↔ Physical function
Johnston, 2009 [36]	Disuse atrophy model (N=7)	Randomized, single blind, crossover	3 wks	↑ LBM, ↑MVC, Exercise output
Sakkas, 2009 [8]	HIV+ men (N=40)	RCT	14 wks + resistance exercise	↑ BW, ↑LBM, ↔MVC↔PCr recovery

Abbreviations: RCT, randomized, double-blind, placebo-controlled clinical trial; CSA, cross sectional area; MVC, Maximum voluntary contraction; LBM, lean body mass; BW, body weight; PCr, phosphocreatine