Biogerontology (2011) 12:273–281
DOI 10.1007/s10522-011-9327-6

REVIEW ARTICLE

Sarcopenia: current theories and the potential beneficial effect of creatine application strategies

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Received: 19 May 2009 / Accepted: 30 October 2009 / Published online: 4 March 2011

Abstract Sarcopenia, defined as the age-related loss of muscle mass, subsequently has a negative effect on strength, metabolic rate and functionality leading to a reduced quality of life. With the projected increase in life expectancy, the incidence of muscle loss may rise and further drain the health care system, with greater need for hospitalization, treatment, and rehabilitation. Without effective strategies to counteract aging muscle loss, a global health care crisis may be inevitable. Resistance training is well established to increase aging muscle mass and strength. However, muscle and strength loss is still evident in older adults who have maintained resistance training for most of their life, suggesting that other factors such as nutrition may affect aging muscle biology. Supplementing with creatine, a high-energy compound found in red meat and seafood, during resistance training has a beneficial effect on aging muscle. Emerging evidence now suggests that the timing and dosage of creatine supplementation may be important factors for aging muscle accretion. Unfortunately, the long-term effects of different creatine application strategies on aging muscle are relatively unknown.

Keywords Aging · Muscle · Strength · Exercise

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Introduction

Sarcopenia, defined as the age-related loss of muscle quantity and quality (Roubenoff 2000; Thompson 2009), subsequently has a negative effect on strength (Evans 1995), muscle protein kinetics (Bales and Ritchie 2002), metabolic rate (Piers et al. 1998), and oxidative capacity (Roubenoff and Hughes 2000) leading to an increase in fat mass (Marzetti et al. 2009) and an impaired ability to perform tasks of daily living such as gardening, carrying groceries, and climbing stairs (Short and Nair 2001). Approximately 25% of individual's ≥70 years of age have established sarcopenia (i.e., loss of muscle mass ≥2 standard deviations below young reference means, Baumgartner et al. 1998) and this proporation increases to 30–50% for individuals ≥80 years of age (Baumgartner et al. 1998; Hepple 2003). The direct and indirect health costs associated with aging muscle loss are estimated to be over $300 billion in the United States alone (Booth et al. 2000). With the projected increase in life expectancy (Bales and Ritchie 2002), the incidence of sarcopenia may rise and further drain the health care system, with greater need for hospitalization, treatment and rehabilitation

(Papadimitropoulos et al. 1997). Without effective strategies to counteract sarcopenia, a global health care crisis in the future may be unavoidable. Therefore, understanding the mechanisms leading to muscle dysregulation during the aging process should be a top public health priority (Thompson 2009). Despite an abundance of literature on aging muscle biology, there remains a paucity of information regarding the underlying mechanism(s) and adaptations of aging. Ultimately, the development of effective strategies to counteract aging muscle loss is entirely dependent on the processes that induce sarcopenia.

Potential pathogenesis of sarcopenia

Muscle morphology

It is estimated that skeletal muscle mass and strength decrease by approximately 1–2% per year after 50 years of age (Hughes et al. 2002; Sehl and Yates 2001). Mechanistically, muscle and force loss with age may be caused by a reduction in muscle fiber number (Hepple et al. 2004; Trappe 2001), although fiber atrophy, particularly among type II fibers, is also involved (Larsson et al. 2001). During the aging process, there is spatial rearrangement of motor unit fibers and an increased number of muscle fibers per motor unit area (Larsson and Salviati 1989). Consequently, total muscle fiber number typically decreases indicating a denervation-reinnervation process (Ansved and Edstrom 1990). In relation to this spatial reorganization of motor unit fibers, changes in myofibrillar protein isoform expression has also been observed both in slow-twitch and fast-twitch muscles. There appears to be a gradual disappearance in fast-twitch (i.e., type II) muscle fibers with age which precedes the age-related loss of total muscle fiber number (Ansved and Larsson 1989). A further fast-to-slow transformation process resulting in an increased number of intermediate (i.e., type IIa) and slow-twitch muscle fibers (i.e., type I) have also been reported (Bass et al. 1975; Boreham et al. 1988) inevitably compromising force production (Hepple 2003).

Satellite cells

Satellite cells are mononucleiated cells which reside between the basal lamina and sarcolemma (Mauro 1961) and appear to have a finite lifespan and undergo replication in the last stage of post-embryonic development (for review see Gopinath and Rando 2008). Once activated (i.e., mechanical stimuli from resistance training), satellite cells produce muscle precursor cells which undergo activation, proliferation and differentiation to form new muscle fibers (Ryall et al. 2008). Satellite cells are essential for muscle growth, repair and maintenance (Hawke and Garry 2001; Mauro 1961). Unfortunately, aging appears to have a negative effect of satellite cell function and quality (for review see Brack and Rando 2007). An attenuation of satellite cell proliferation could potentially limit aging muscle hypertrophy, especially if satellite cells proliferative potential is exhausted during a lifespan of repeated cycles of atrophy and re-growth (Chakravarthy et al. 2001). In addition, aging satellite cells exhibit a delayed response to mechanical stimuli (i.e., resistance training) and are susceptible to cellular apoptosis (Jejurikar et al. 2006). Recent research also has shown a substantial reduction in the number of active satellite cells in type II but not type I fibers of the vastus lateralis in older adults (Verdijk et al. 2007); suggesting that satellite cell attenuation with age are fiber specific which may help explain the reduction in type II muscle fibers.

Muscle contraction

Regarding muscle contractile properties, the age-related slowing of twitch properties in motor units of both fast-twitch and slow-twitch muscle fibers is thought to be caused by structural (DeCoster et al. 1981), functional (Larsson and Salviati 1989), and biochemical (Viner et al. 1996) changes in the sarcoplasmic reticulum. Sarcoplasmic reticulum properties are the strongest determinants of speed of contraction whereas myosin heavy chain isoforms influence maximum shortening velocity (Brody 1976). It has been shown that the aging process has a negative effect on sarcoplasmic reticulum protein quality and function (Larsson et al. 2001), resulting in a decline in maximum contractile force in skeletal muscle. Furthermore, there is a significant reduction in myosin per muscle fiber volume with age (Marx et al. 2002; Thompson 2009). Myosin is the main myofibrillar protein responsible for force production in skeletal muscle. Using a rat model, Larsson et al.

(2001) found a two-fold decrease in speed of contraction between old and young isolated muscle fibers suggesting an accelerated decline in myosin function with aging.

Muscle protein and hormonal kinetics

Skeletal muscle is a dynamic tissue undergoing constant protein turnover (i.e., protein catabolism and protein synthesis; for review see Rennie and Tipton 2000). For muscle hypertrophy to proceed, the synthetic rate of muscle proteins must be greater than the breakdown rate of muscle proteins (Rennie and Tipton 2000). During the aging process, there is accelerated protein catabolism (i.e., whole-body, mixed-muscle,) resulting in muscle tissue atrophy (Karakelides and Nair 2005; Marcell 2003) and subsequent infiltration of fat and connective tissue, possibly because of decreased sensitivity to amino acids, insulin, or both (Combaret et al. 2009). Research has shown that the basal rate of myofibrillar, mixed, and mitochondrial protein synthesis is substantially reduced in older adults (Balagopal et al. 2001; Katsanos et al. 2006; Rooyackers et al. 1996). Furthermore, a decrease in anabolic hormone production of testosterone (Baumgartner et al. 1999), growth hormone (Welle et al. 1996), and insulin growth factor-1 (Butterfield et al. 1997), and an increase in cortisol may play a role in the pathogenesis of sarcopenia (for review see Marcell 2003) by inhibiting the capacity of skeletal muscle to incorporate amino acids into muscle proteins (Deschenes 2004).

Oxidative stress

A decrease in oxidative homeostasis has also been implicated in contributing to aging muscle loss (for review see Johnston et al. 2008). The 'mitochondrial' or 'oxidative stress' theory of aging suggests there is a progressive cellular decline with aging due to the accumulation of damage by mutagenic oxygen radicals (i.e., reactive oxygen species) to cellular components resulting in cellular senescence (Johnston et al. 2008; Sohal and Weindruch 1996). Elevated oxidative damage upregulates antioxidant systems and with aging, may not be able to overcome oxidative cellular stress. Coincidently, cytokines are released in response to chronic inflammation and stress (i.e., resistance training), and aging results in an accelerated increase in the release of the pro-inflammatory cytokines interleukin 6 (IL-6) and tumor necrosis factor-α (TNF-α). An age-related increase in IL-6 and TNF-α have been shown to result in muscle atrophy, strength loss (Bautmans et al. 2005; Ladner et al. 2003) and muscle protein catabolism (Bales and Ritchie 2002).

Creatine and aging

Creatine is a guanidine-derived compound naturally produced in the body (i.e., 1-2grams/day; see Walker 1979) from reactions involving the amino acids glycine, arginine, and methionine (for review see Wyss and Kaddurah-Daouk 2000) and consumed in the diet from red meat and seafood (i.e., 1-2grams/day; see Lykken et al. 1980). Very little creatine is retained at the site of production. The majority of creatine is transported from areas of synthesis (i.e., liver, kidney) to areas of storage and utilization (i.e., skeletal muscle; Persky and Brazeau 2001). Skeletal muscle accounts for approximately 95% of all creatine stores in the body (Green et al. 1996; Greenhaff et al. 1993). Creatine uptake is facilitated by the creatine transport protein, CreaT (Guerrero-Ontiveros and Wallimann 1998). CreaT expression matches that of creatine kinase (CK): high in areas of creatine storage and utilization (i.e., skeletal muscle) and low in areas of creatine synthesis (i.e., liver, kidney, pancreas). Skeletal muscle creatine content is dependent on muscle fiber composition (Smith et al. 1998). Type II muscle fibers, which decrease with age (Larsson et al. 2001), have high levels of free creatine (Cr) and phosphocreatine (PCr) which is needed to resynthesize adenosine diphosphate (ADP) and maintain adenosine triphosphate (ATP) during muscle contraction Increasingly, there is research showing a positive effect from creatine supplementation on muscle accretion in the aging population (Table 1). With age, there is a progressive decrease in muscle mass (Evans 1995; Roubenoff 2003). Potentially, reduced high-energy phosphate metabolism may play a role in these metabolic changes with age. Since 90–95% of PCr is housed in skeletal muscle (Sipilä et al. 1997), it is logical to assume that a progressive decrease in muscle mass with age would be associated with a reduction in PCr (Candow and Chilibeck 2008). An increase in intramuscular creatine (i.e., PCr and Cr) from creatine supplementation should

Table 1 Summary of studies involving creatine supplementation in older adults

Study	Population	Dosage	Findings
Bermon et al. 1998	Male/female (70 years) CR: 16; PL: 16	CR: 20 g for 5 days Maintenance: 3 g for 47 days	↔ lower-limb muscle volume
Brose et al. 2003	Male/female (68 years) CR: 14; PL: 14	CR: 5 g, 98 days	↑ fat-free mass
Candow et al. 2008	Male (66 years) CR: 23; PL: 12	CR: 0.1 g kg^{-1}, 30 days	↑ muscle hypertrophy
Chrusch et al. 2001	Male (71 years) CR: 16; PL: 14	CR loading: 0.3 g kg^{-1} for 5 days Maintenance: 0.07 g kg^{-1} for 79 days	↑ fat-free mass, strength
Eijnde et al. 2003	Male (64 years) CR: 23; PL: 23	CR: 5 g for 1 year	↔ fat-free mass
Gotshalk et al. 2008	Female (63 years) CR: 15; PL: 12	CR: 0.3 g kg^{-1} for 7 days	↑ fat-free mass, strength
Gotshalk et al. 2001	Male (65 years) CR: 10; PL: 8	CR: 0.3 g kg^{-1} for 7 days	↑ fat-free mass
Jakobi et al. 2001	Male (72 years) CR: 7; PL: 5	CR : 20 g for 5 days	↔ force production
Rawson et al. 1999	Male (74 years) CR: 10; PL: 10	CR: 20 g for 10 days Maintenance: 4 g for 20 days	↔ fat-free mass
Tarnopolsky et al. 2007	Male/female (70 years) CR: 21, PL: 18	CR: 5 g/days for 6 months	↑ fat-free mass, strength

CR creatine, *PL* placebo

theoretically increase PCr resynthesis during muscle contraction leading to greater exercise training intensity and subsequently muscle mass (Chrusch et al. 2001). For example, creatine supplementation (0.1 g kg^{-1}) only on training days during 10 weeks of structured resistance training (3 sets of 10 repetitions, 3 days/week; 9 exercises) increased whole-body muscle hypertrophy (2.0 ± 0.3 cm) compared to placebo (0.8 ± 0.3 cm) and resistance training in healthy older males (59–77 years; Candow et al. 2008). Brose et al. (2003) found a significant increase in intramuscular total creatine leading to greater muscle accretion (1.7 ± 1.2 kg) in healthy older adults from creatine supplementation (5 g day^{-1}) during 14 weeks of resistance-training (3 sets of 10–12 repetitions, 12 exercises, 3 days/week). Furthermore, Chrusch et al. (2001) reported increases of 3.3 kg for lean tissue mass, 50.1 kg for leg press strength, and 14.9 kg for knee extension strength following 12 weeks of creatine supplementation (0.3 g kg^{-1} × 5 days; 0.07 g kg^{-1} for 79 days) and resistance training (3 sets of 10 repetitions, 3 days/week, 12 exercises) in healthy older men (59–77 years). The older men who consumed creatine were able to exercise with 31% greater training volume (i.e., load × repetitions × sets) compared to placebo. These results support the short-term findings of Gotshalk et al. (2002, 2008) who found a significant increase in fat-free mass (2.2 ± 0 kg) in healthy older men (59–72 years) and an increase in fat-free mass (0.5 ± 0.05 kg), bench press (1.7 ± 0.4 kg) and leg press strength (5.2 ± 1.8 kg) in healthy older females (58–71 years) after 7 days of creatine supplementation (0.3 g kg^{-1}).

The mechanistic actions explaining the increase in muscle mass and strength from creatine supplementation remain to be determined. However, it has been theorized that creatine has the ability to regulate osmosis within the working cell and could potentially elevate intracellular osmolarity (Balsom et al. 1995). The anabolic signal induced by cellular hydration may increase the expression of myogenic transcription factors such as myogenin and MRF-4 (Balsom et al. 1995; Francaux and Poortmans 1999; Kreider et al. 1998) or alter the level of charged tRNAs which are specific for myofibrillar protein synthesis (Ingwall et al. 1974). Myogenic transcription factors initiate

transcription and regulate gene expression by binding to specific regions of a DNA sequence located on the promoter and enhancer regions downstream of muscle specific genes such as myosin heavy chain (Willoughby and Rosene 2003). Potentially, creatine may increase the expression of these transcription regulators and augment the up-regulation of muscle specific-genes such as myosin heavy chain, thereby facilitating an increase in muscle hypertrophy and strength (Willoughby and Rosene 2003). For example, creatine supplementation (20 g day^{-1}) in young healthy adults during 2 weeks of leg immobilization, followed by 10 weeks of rehabilitation training, increased the expression of MRF-4. The change in MRF-4 expression was correlated with an increase in muscle cross-sectional area (Hespel et al. 2001). In addition, creatine supplementation (6 g day^{-1}) during 12-weeks of heavy resistance training significantly increased mRNA and protein expression of myogenin and MRF-4 in young male subjects (Willoughby and Rosene 2003). Theoretically, creatine supplementation may increase mRNA template availability in muscle undergoing hypertrophy, resulting from changes in transcriptional capacity, translational efficiency, and/or mRNA stability (Rennie et al. 2004). Furthermore, creatine supplementation has been shown to increase satellite cell mitotic activity (Dangott et al. 2000), proliferation in vitro (Vierck et al. 2000) and content in young males engaged in resistance training for 16 weeks (Olsen et al. 2006). The increase in satellite cell activity and content would be expected to increase mRNA transcription and subsequently increase muscle protein synthesis leading to muscle hypertrophy over time (Kadi 2000). However, in contrast to these positive findings from creatine, Bermon et al. (1998) failed to observe an increase in lower limb muscle mass after 8 weeks of creatine supplementation and resistance training in older men and women. Furthermore, creatine supplementation for up to 1 year failed to increase fat free mass in older men (Eijnde et al. 2003). In other studies, creatine supplementation in older males did not improve physical performance, muscle mass (Rawson et al. 1999; Rawson and Clarkson 2000), or neuromuscular fatigue (Jakobi et al. 2001). Based on these equivicol results, future studies will have to determine the potential of creatine supplementation to influence intracellular cell volume, gene expression, satellite cell activity, and muscle protein turnover in older individuals.

Strategic creatine ingestion

Muscle hypertrophy following resistance training requires net synthesis of myofibrillar proteins and therefore, maximal stimulation of muscle protein synthesis is required for the development of muscle mass in older adults (Candow et al. 2006; Esmarck et al. 2001). It is well established that the mechanical stimulus from resistance training results in increased protein catabolism and subsequent protein synthesis (Phillips 2004). Although the machinery for stimulating the synthetic rate of muscle proteins is increased after exercise (Welle and Thornton 1998), it appears that this response may not be increased until some time after the resistance training session (Tipton et al. 2001). The timing of creatine supplementation may be crucial for creating an anabolic environment for muscle growth (for review see Candow and Chilibeck 2008). Recent evidence suggests that creatine ingestion, in close proximity to resistance training sessions (i.e., before and after exercise), may be more beneficial than ingesting creatine at other times of the day (i.e., morning and evening). For example, consuming creatine immediately before (0.05 g kg^{-1}) and immediately after (0.05 g kg^{-1}) resistance training sessions (3 days/week, 10 weeks) resulted in greater whole-body muscle hypertrophy (2.0 $\pm$ 0.3 cm) compared to placebo (0.8 $\pm$ 0.3 cm) and resistance training in healthy older males (59–77 years; Candow et al. 2008). Older adults supplementing with creatine also had a reduction in urinary excretion of 3-methylhistidine, an indicator of muscle protein catabolism, by 40% compared to an increase of 29% for the placebo group; suggesting that creatine exhibits muscle anti-catabolic properties in older adults. 3-methylhistidine is an amino acid found in actin and the heavy chain of myosin in skeletal muscle (Rennie and Millward 1983) and when measured in urine, is considered to be an indicator of skeletal muscle catabolism (Frontera et al. 1988; Lukaski et al. 1981). These results support previous findings of a significant increase in lean tissue mass (6%), type II muscle fiber area (29%), and insulin growth-factor I (78%) in adults (19–55 years) who ingested creatine before (0.03 g kg^{-1}) and after (0.03 g kg^{-1}) resistance training (6 days/week, 8 weeks; see Burke et al. 2003, 2008). In addition, young adults (22–26 years) who supplemented with creatine (0.2 g kg^{-1}) immediately after performing resistance training (2 days/week, 6 weeks) experienced a greater gain in elbow flexor muscle thickness

(0.36 ± 0.06 cm or 10.3%) compared to consuming placebo immediately after training (0.24 ± 0.07 cm or 6.3%; Chilibeck et al. 2004). Interestingly, in comparing the effects of creatine ingestion before (0.5 g kg^{-1}) and after (0.5 g kg^{-1}) resistance training (10 weeks) to creatine ingestion in the morning and evening of training days, Cribb and Hayes (2006) showed that creatine ingestion before and after exercise resulted in significantly greater intramuscular creatine content, lean tissue mass, and muscle cross sectional-area of type II fibers. Although it is difficult to compare results across studies, it has been theorized that these positive results from creatine ingestion before and after exercise may be due to an increase in blood flow and delivery of creatine to exercising muscles (Harris et al. 1992), an upregulation of the kinetics involved in creatine transport (Robinson et al. 1999), and by an increase in Na^+–K^+ pump function during exercise (Robinson et al. 1999).

Summary and future considerations

Sarcopenia is a major health concern and has a negative effect on functionality and quality of life. Resistance training is a strategy often recommended for older adults to preserve and/or increase muscle mass and strength. In addition to exercise, creatine supplementation has been shown to increase muscle mass and strength in the older population. However, the timing of creatine ingestion (i.e., 0.03–0.5 g kg^{-1} before and after resistance training sessions) may be more important than the quantity of creatine. These novel findings have immediate application for research and health professionals for the design of optimal creatine application strategies for older individuals. For example, emphasizing commercial creatine or food products that contain dietary creatine (i.e., red meat, seafood) in close proximity to resistance training sessions may augment muscle mass and strength to a greater extent than resistance training alone. Future research should investigate the mechanistic actions of long-term creatine supplementation, independent of resistance training, on aging muscle biology.

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