Timing of creatine or protein supplementation and resistance training in the elderly

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Abstract: Muscle loss with age has a negative effect on strength and functional independence. Age-related loss of muscle is the result of decreased muscle fiber number and size, which are functions of altered hormonal status, physical inactivity, and variations in nutritional intake. Resistance training has a positive effect on muscle mass and strength in the elderly. Studies of protein or creatine supplementation for increasing muscle mass and strength in older individuals are equivocal. The timing of nutritional supplementation may be more important than the absolute daily intake of supplements. Protein or creatine ingestion proximate to resistance-training sessions may be more beneficial for increasing muscle mass and strength than ingestion of protein or creatine at other times of the day, possibly because of increased blood flow and therefore increased transport of amino acids and creatine to skeletal muscle.

Key words: muscle mass, hypertrophy, strength, sarcopenia, aging.

Introduction

The loss of muscle mass with age has a negative effect on strength, functional independence, and quality of life (Candow and Chilibeck 2005; Lindle et al. 1997; Porter et al. 1995; Walsh et al. 2006). An age-related decline in muscle is a result of reduction in size and (or) number of muscle fibers (Lexell 1993). The reduction in muscle fiber size and number may be a function of hormone status, inactivity, or under-nutrition (Evans 2004).

Resistance training is well known to have a positive effect on muscle mass in the aging population. However, muscle atrophy is still observed in older adults who regularly per- form resistance-type exercise (Hameed et al. 2002; Starling et al. 1999; Trappe 2001). Therefore, other factors such as nutrition must contribute to the age-related loss in muscle. Although the majority of age-related research has focused on the quantity of nutritional intervention during resistance training, the purpose of this review is to highlight recent advances suggesting that the timing of nutritional intervention during resistance training may be important. Specifically, we review studies of creatine supplementation during resistance training in older individuals and then review studies that emphasize the timing of protein or creatine supplementation, rather than the daily quantity of these supplements.

There is controversy as to whether protein supplementation is beneficial for the elderly and would augment adaptations to resistance training. Currently, the recommended dietary allowance (RDA) for dietary protein is 0.8 g·kg body mass\(^{-1}\)·d\(^{-1}\) for individuals 51 years and older (Institute of Medicine of the National Academies and the Food and Nutrition Board 2005). A recent review suggests that protein needs of older individuals are highly variable and recommends an intake of 1.0 to 1.3 g·kg\(^{-1}\)·d\(^{-1}\) for those engaged in resistance training (Lucas and Heiss 2005). Sedentary
older adults placed on diets providing 0.8 g·kg\(^{-1}\)·d\(^{-1}\) protein had reductions in muscle cross-sectional area (Campbell et al. 2001, 2002) and whole-body fat-free mass (Campbell et al. 2002) and went into negative nitrogen balance (Campbell et al. 1995), suggesting protein needs of older individuals may be higher than the RDA. However, when these individuals were placed on a resistance-training program, efficiency of nitrogen retention increased so that body composition changes were similar to older adults consuming a high-protein diet (i.e., 1.6 g·kg\(^{-1}\)·d\(^{-1}\) (Campbell et al. 1995). In contrast, a more recent study indicated that older adults engaging in resistance training and consuming 0.8 g·kg\(^{-1}\)·d\(^{-1}\) protein lost fat-free mass over a period of 12 weeks, suggesting that the RDA for protein might be marginally inadequate for older people to maintain muscle mass (Campbell et al. 2002). The breakdown of contractile protein during resistance-type training suggests that protein needs may exceed basal levels (Rennie and Tipton 2000). Amino acid ingestion at rest, before, and after exercise increases protein synthesis and attenuates protein breakdown (Tipton et al. 2001; Wolfe 2001), possibly through an increase in translational efficiency. Therefore, it has been suggested that an increase in amino acid availability from additional dietary protein may augment the hypertrophic response from resistance-training sessions leading to greater muscle mass over time. Some studies of protein supplementation during resistance training in older adults show a beneficial effect (Bos et al. 2000; Esmarck et al. 2001; Meredith et al. 1992), whereas others have not observed the same benefits (Andrews et al. 2006; Candow et al. 2006b; Godard et al. 2002; Welle and Thornton 1998). These inconsistent findings across studies may be the result of individual differences in nutritional status, habitual dietary protein intake, health, and disease.

Creatine monohydrate is among the most widely used and researched ergogenic aids to date (Jacobs 1999). Creatine is readily found in red meat and seafood and is endogenously synthesized by humans in the liver and pancreas. Phosphocreatine (PCr) plays an important role in supporting metabolism during high-intensity exercise and impairments in PCr metabolism may therefore hinder muscle performance and reduce muscle mass (Heinanen et al. 1999; Levine et al. 1996). There is conflict in the literature as to whether PCr metabolism is negatively affected by age. Some studies indicate older individuals have decreased intramuscular PCr stores (Forsberg et al. 1991; Moller et al. 1980) and impaired metabolism of high-energy phosphates (i.e., slower PCr resynthesis; Smith et al. 1998), whereas others show intramuscular PCr levels may actually be higher in older individuals (Rawson et al. 2002) and that aging has no effect on PCr metabolism (Chilibeck et al. 1998). A few studies have reported that creatine supplementation during resistance training increases muscle mass and muscular strength, endurance, and power in older individuals (Brose et al. 2003; Chrusch et al. 2001), but there are other studies showing no beneficial effect from creatine supplementation during resistance training (Bermon et al. 1998; Eijnde et al. 2003). A number of studies indicate creatine supplementation without resistance training in older adults has minimal benefits (Jakobi et al. 2001; Rawson et al. 1999; Rawson and Clarkson 2000). For older individuals to respond to creatine supplementation, it may have to be in conjunction with resistance training. Increased exercise performance and muscle hypertrophy with creatine supplementation during resistance training may occur through enhanced high-energy phosphate metabolism (Brose et al. 2003), increased cellular hydration status (Balsom et al. 1995), activation of myogenic regulatory factors (Willoughby and Rosee 2003), satellite cell proliferation (Olsen et al. 2006), and decreased protein breakdown (Chilibeck et al. 2007; Parise et al. 2001).

**Resistance training and supplementation with protein or creatine**

Muscle accretion reflects the net balance between muscle protein synthesis and protein breakdown (Balagopal et al. 1997). Muscle loss may be the result of a decrease in protein synthesis, an increase in protein breakdown, or both (Tipton et al. 2001). Older men and women (>60 years) have significant reductions in muscle mass (Deschenes 2004), whole-body protein synthesis, and myofibrillar protein synthesis (Welle et al. 1994), with a loss of strength of approximately 30%–40% after the 3rd decade (Schulte and Yarasheski 2001). Resistance-type training can reduce some of these deficits (Schulte and Yarasheski 2001; Tipton 2001). For example, untrained volunteers (aged 60–72 y) who performed isokinetic knee extension and flexion exercise for 12 weeks had significant gains in muscle cross-sectional area and muscle protein turnover (Frontera et al. 1988). Even in the frail elderly (aged 90–92 y), independent of nutritional status, 8 weeks of intense resistance training significantly increased knee extensor muscle mass (Fiatarone et al. 1990). These changes contribute to substantial increases in strength (i.e., up to approximately 100%–200% depending on initial training status) in relatively short periods of time (Fiatarone et al. 1990, 1994; Singh et al. 1999; Yarasheski et al. 1993).

Research is controversial regarding the effect of additional dietary protein when combined with resistance training in the elderly. Although muscle protein turnover may be reduced in older individuals, (Campbell et al. 1995; Welle et al. 1994), the capacity to respond to resistance training and additional dietary protein may be similar to that of the young, depending on nutritional status (Rennie and Tipton 2000). For example, older males (aged 61–72 y) who supplemented with protein (~24 g·d\(^{-1}\)) during 12 weeks of knee flexor and extensor strength training experienced greater gains in midthigh muscle mass over strength training alone (Meredith et al. 1992) and frail elderly receiving a dietary supplement (360 kcal; 17% protein) had greater gains in strength and muscle fiber cross-sectional area than those not taking nutritional supplementation (Singh et al. 1999). In contrast to these findings, Godard et al. (2002) found no beneficial effect from amino acid supplementation after knee extension exercise for 12 weeks, either on whole-muscle strength or muscle cross-sectional area, in healthy older adults. In addition, healthy older men and women (aged 62–75 y) who increased dietary protein intake during unilateral knee extension exercise had no greater increase in myofibrillar protein synthesis over exercise alone (Welle and Thornton 1998), suggesting that the additional amino acids were not being incorporated into muscle protein. The
authors speculated that this slower rate of protein synthesis may be caused by a reduction in translational efficiency in older muscle. These equivocal results across studies have led to speculation that the quantity of dietary protein during resistance training may not be a key regulator for increasing muscle mass in older individuals, except perhaps for those who are deficient in dietary protein intake (Evans 2004).

Research showing a positive effect from creatine supplementation in the aging population is equivocal with some showing a benefit from acute or long-term supplementation (Brose et al. 2003; Candow et al. 2004; Chilibeck et al. 2005; Chrusch et al. 2001; Gotshalk et al. 2002; Rawson et al. 1999), whereas others show no benefit (Bermon et al. 1998; Eijnde et al. 2003; Jakobi et al. 2001; Rawson et al. 2002). The age-related reduction in muscle mass may partially be the result of a reduced exercising capacity from lower PCR stores (Forsberg et al. 1991; Moller et al. 1980) or altered high-energy phosphate metabolism (Smith et al. 1998); however, some studies indicate no reductions in intramuscular PCR or alterations in metabolism with aging (Bermon et al. 1998; Chilibeck et al. 1998). Creatine supplementation increases intramuscular total creatine (i.e., creatine and PCR) in older individuals (Brose et al. 2003; Eijnde et al. 2003) and the increase in PCR may possibly allow one to train with a greater volume of resistance exercise leading to muscle accretion. For example, healthy older males supplementing with creatine during 14 weeks of resistance training experienced a greater increase in PCR; whole-body fat-free mass, and lower-limb muscle strength over placebo and resistance training (Brose et al. 2003). Furthermore, older individuals engaged in resistance training were able to train with 31% higher volume (defined as sets × reps × kilograms lifted) over 12 weeks when taking creatine supplementation than when taking a placebo (Chrusch et al. 2001). In contrast, older males who supplemented with creatine during resistance training for 6 months experienced no increase in PCR, muscle strength, or exercise training capacity over placebo (Eijnde et al. 2003). Therefore, an increase in PCR from creatine supplementation may be required for increasing muscle mass and strength in older individuals. Despite this potential for an ergogenic effect from creatine, studies that have combined creatine supplementation during resistance training programs for older individuals are equivocal on whether creatine supplementation provides benefits beyond resistance training alone, with 2 studies showing a benefit (Brose et al. 2003; Chrusch et al. 2001) and 2 studies showing no benefit (Bermon et al. 1998; Eijnde et al. 2003). Chrusch et al. (2001) supplemented men (70 y) with ~26 g·d⁻¹ creatine for 5 d (loading phase) and ~6 g·d⁻¹ thereafter during 12 weeks of whole-body resistance training (3 sets of 10 repetitions, 10 exercises, 3 d·week⁻¹). Creatine supplementation increased measures of lean tissue mass, strength, muscular endurance, and muscular power over placebo. Brose et al. (2003) supplemented men and women (65 y) with 5 g·d⁻¹ creatine during 14 weeks of whole-body training (3 sets of 10–12 repetitions, 12 exercises, 3 d·week⁻¹). Creatine supplementation again increased some measures of strength and lean tissue mass over placebo. On the other hand, Bermon et al. (1998) found no advantage with creatine supplementation (20 g·d⁻¹ for 5 d and 3 g·d⁻¹ thereafter) during 8 weeks of resistance training in males and females (67–80y). Their group sizes were small (i.e., 16 men and 16 women randomized to 4 groups: control–creatine, control–placebo, training–creatine, and training–placebo); therefore, their study lacked statistical power. In addition, their training volume was quite low (3 sets of 8 repetitions for 3 exercises, 3 d·week⁻¹) compared with studies that showed a positive effect of creatine during training (Brose et al. 2003; Chrusch et al. 2001), and none of their groups increased muscle mass. Similar to Bermon et al. (1998), Eijnde et al. (2003) found no effect from creatine (5 g·d⁻¹) on muscular strength or lean-tissue mass during a 1 y training program in men aged 55–75 y. Again, their training program differed substantially from studies showing a benefit from creatine. Their program involved 2 sets of 30 repetitions for 7 exercises, 2–3 d·week⁻¹, of which only 2 exercises (leg extension and arm curl) were “obligatory” for their men to perform. Their program therefore involved “muscular endurance” training, rather than strength training, and had a minimal effect on lean-tissue mass. The men in their study may have been less responsive to creatine supplementation because their intramuscular creatine levels were relatively high at baseline (i.e., PCR = 91 mmol·kg dry mass⁻¹; total creatine = 135 mmol·kg dry mass⁻¹), whereas men in the study of Brose et al. (2003) who had improved lean-tissue mass and muscular performance during creatine supplementation had lower baseline levels (i.e., PCR = 67 mmol·kg dry mass⁻¹; total creatine = 117 mmol·kg dry mass⁻¹). We have previously shown that individuals with lower baseline intramuscular total creatine levels are more responsive to creatine supplementation during resistance training (Burke et al. 2003). Eijnde et al. (2003) had their participants consuming only 3 g creatine (of the 5 g·d⁻¹) in close proximity to their training sessions. Recently, it has become apparent that creatine supplementation may be most beneficial if ingested in close proximity to training sessions (i.e., immediately before or immediately after) rather than at other times of the day (Cribb and Hayes 2006). In the next section we review the potential benefits of consuming protein or creatine supplements in close proximity to training sessions and recent studies indicating this may be effective for older individuals.

**Timing of nutritional intervention**

The timing of nutritional intervention may be crucial for creating an anabolic environment for muscle hypertrophy (Andersen et al. 2005; Candow et al. 2006a; Chilibeck et al. 2004; Cribb and Hayes 2006; Esmarck et al. 2001; Roy et al. 2000; Tipton et al. 2001). Muscle hypertrophy following resistance training requires net protein synthesis of myofibrillar proteins. It is well known that resistance training results in increased protein degradation and protein synthesis. The rate of protein synthesis exceeds the rate of protein degradation when protein or amino acids are ingested at rest (Biolo et al. 1997). As protein ingestion is important for creating an optimal effect on net muscle protein synthesis, intake of protein before and after exercise is likely important. During resistance training, there may be a net loss of muscle protein, because muscle protein degradation is elevated (Rennie et al. 1981), whereas protein synthesis is usually decreased (Bylund-Fellenius et al. 1984). Although the signal-
The strategy of ingesting protein in close proximity to exercise has recently been evaluated in older individuals. Postmenopausal women who ingested a protein–carbohydrate supplement after knee extension resistance exercise had an increased nitrogen balance after exercise compared with those who ingested a placebo (Holm et al. 2005). Older males (~74 y) who ingested protein (~10 g) immediately after resistance-training sessions over a 12 week period experienced significant gains in muscle cross-sectional area, mean fiber area, and muscular strength over subjects who ingested protein 2 h post-exercise (Esmarck et al. 2001). However, no comparison of protein supplementation before versus after resistance training was performed. Recently, we found that protein supplementation (0.3 g·kg body mass\(^{-1}\); ~25 g) immediately before resistance-training sessions over a period of 12 weeks was more effective for inducing hypertrophy of the knee extensors than consuming an equivalent amount of protein after the resistance-training session (Candow et al. 2006b; Fig. 2). This corresponds with the findings of Tipton et al. (2001) in young individuals—that amino acid supplementation immediately before a resistance-training session resulted in greater protein synthesis post-exercise, in the same muscle group (i.e., the knee extensors), compared with ingestion of amino acids after exercise. However, we found no benefit of consuming protein before or after training in older men on any other measure of muscle hypertrophy (i.e., knee flexors, elbow and ankle flexors and extensors), whole-body lean-tissue mass, or muscular strength. Based on our findings and those of Tipton et al. (2001) we conclude that protein ingestion before exercise sessions offers a small advantage, possibly through increased amino acid delivery to muscle owing to exercise-increased blood flow.

Creatine ingestion in close proximity to exercise-training sessions may also be more beneficial than ingesting creatine at other times of the day, again because of increased blood flow and delivery of creatine to muscle or perhaps through co-transport of creatine into muscle when the sarcoplasmic sodium–potassium pump is activated (Harris et al. 1992; Robinson et al. 1999). In young individuals, muscle hypertrophy was promoted specifically in muscle groups exercised immediately before creatine supplementation during a 6 week resistance-training program (Chilibeck et al. 2004). Consuming creatine and protein immediately before and after resistance training in older men. Asterisk (*) indicates percent change for Protein Before is significantly greater than Placebo, p < 0.05.
after resistance training sessions for 10 weeks resulted in greater increases in muscle cross-sectional area, contractile protein, and muscular strength compared with consuming the supplement in the morning and evening (Cribb and Hayes 2006). Although these studies showed an ergogenic effect from creatine and protein in young adults, research in the elderly is limited. We recently showed that healthy older males who supplemented with protein (0.1 g kg body mass⁻¹) and creatine (0.03 g kg body mass⁻¹) before and after whole-body resistance-training sessions for 10 weeks experienced greater gains in muscle mass over creatine alone or placebo (Candow 2005). Individuals supplementing with creatine also had a reduction in urinary 3-methylhistine, an index of myofibrillar protein catabolism, compared with placebo (i.e., a reduction of 40% with creatine compared with an increase of 29% with placebo; Chilibeck et al. 2007). Based on these findings across studies, it appears that strategic ingestion of creatine and protein supplementation before and after resistance-training sessions may lead to greater muscle hypertrophy in young and older individuals.

Summary and future directions

The effectiveness of creatine or protein supplementation during resistance training in the elderly is equivocal, with some studies indicating a benefit from supplementation and some studies showing no benefit above resistance training alone. The timing of nutritional intervention may be important for enhancing the hypertrophic response from a regular resistance-training session in the elderly. Protein and creatine supplementation immediately before or immediately after resistance training sessions results in enhanced muscle hypertrophy in the elderly, possibly because of increased blood flow and delivery of amino acids and creatine to muscle. This has importance for the prevention of age-related sarcopenia. Future research should examine the physiological mechanisms of how creatine and protein may impact muscle mass in the elderly. In addition, the safety of long-term creatine and protein supplementation during resistance-exercise training should be determined.

Acknowledgements

D.G. Candow was supported by a Research Grant from Experimental and Applied Sciences, Inc.

References


