Creatine Monohydrate Supplementation and Resistance Training in Older Adults

Creatine Monohydrate Supplementation And Resistance Training in Older Adults

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ABSTRACT

BACKGROUND: Creatine monohydrate (CrM) supplementation during resistance exercise results in a greater increase in fat free mass (FFM), total body mass (TBM), and strength in young men and women. The purpose of the present investigation was to examine the interactive effects of creatine supplementation and resistance training on body composition, strength, and intramuscular total creatine concentration in older men and women.

METHODS: Twenty-eight older men and women were randomly allocated, in a double blind fashion, to receive either CrM (n=14; CrM: 5g + 2g dextrose) or placebo (n=14; PL: 7g dextrose). Subjects participated in a 14 wk progressive, whole-body resistance training program. Pre- and post-training measurements included: 1 RM strength, isometric strength, body composition (TBM, FFM, %BF), muscle fiber area, and muscle total creatine and phosphocreatine.

RESULTS: Training resulted in an increase in 1 RM strength for each of the 4 exercises (range = 26 – 60%) ($p < 0.001$), an increase in knee and dorsiflexion isometric strength ($p < 0.001$) and an improvement of performance on functional tasks ($p < 0.001$). Knee isometric strength was increased more for CrM (46.2%) as compared to PL (22.5%) ($p < 0.05$). Total body mass and lean body mass increased more for CrM (TBM: +1.2 kg; LBM: +1.7 kg) as compared to PL (TBM: -0.2 kg; LBM: 0.4 kg) ($p < 0.05$)

CONCLUSIONS: We conclude that CrM supplementation results in a greater increase in isometric knee extensor strength, total body mass and lean body mass during resistance training in older adults.

KEY WORDS: strength training, exercise, creatine monohydrate, older adults, functional tasks

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

BACKGROUND

1.1 Introduction

Aging is a complex process associated with a general decline in a number of biological systems which eventually manifest in a decreased capacity for the body to function properly. However, sophisticated medical techniques and advanced health care have led to an increased life expectancy among North Americans (Schneider and Guralnik, 1990), and consequently, the study of changes that occur with advancing age are becoming more important.

Sarcopenia, the loss of muscle mass with age, is becoming recognized as a major cause of disability and morbidity in the elderly (Evans and Campbell, 1993; Rosenberg, 1989). Decrements in muscle mass and muscle strength that occur with aging result in altered mobility, physical disability and frailty, and a loss of independence (Whipple et al., 1987). From a practical economic standpoint, these deficits contribute significantly to escalating health care costs. Resistance training has been shown to slow and/or reverse age-related losses in strength (Charette et al., 1991; Fiatarone et al., 1990; Frontera et al., 1988) and, consequently, maintain or increase independent living (Fiatarone et al., 1990).

Creatine monohydrate is a natural substance produced by the liver and is commonly consumed in a carnivorous diet. In recent years, a growing interest in the use of creatine monohydrate as an anabolic intervention for augmenting muscle strength, mass, and function has been examined in healthy individuals (Greenhaff et

et al., 1997), fat free mass (Mihic et al., 2000), muscle strength (Earnest et al., 1995; Maganaris and Maughan, 1998), and exercise performance (Balsom et al., 1993; Birch et al., 1994; Casey et al., 1996; Harris et al., 1993) in healthy young men. Moreover, in response to resistance training, there is a greater increase in fat free mass and strength in those who are given creatine monohydrate as compared to placebo (Kreider et al., 1998; Vandenberghe et al., 1997; Volek et al., 1999).

Advancing age is often associated with a decrease in intramuscular total creatine content (Campbell et al., 1999; Smith et al., 1998). This may make older adults ideal candidates for creatine supplementation, especially since the beneficial effects of this substance on exercise performance are likely to be inversely proportional to the total creatine content in skeletal muscle (Greenhaff et al., 1994; Tarnopolsky et al., 1997). These observations indicate that creatine supplementation in an older population may attenuate or reverse some of the fundamental pathophysiological processes associated with aging (Tarnopolsky, 2001).

The first part of this review discusses a) the age-related alterations in the skeletal-muscular system; b) hormonal changes associated with aging; and c) the effects of resistance training as a preventive measure against sarcopenia. The second part of this review discusses the effects of creatine supplementation and the potential benefits of creatine supplementation in an older population.

PATHOPHYSIOLOGY OF AGING

1.2 Age Associated Changes in Body Composition

Advancing age is associated with alterations in body composition, including a progressive decrease in fat free mass (FFM) and a corresponding increase in fat mass (Cohn et al., 1976; Novak, 1972). The age-related loss of skeletal muscle mass has been termed sarcopenia (Evans and Campbell, 1993; Rosenberg, 1989). Using 24-hour urinary creatinine excretion, an indirect measure of total muscle mass, Tzankoff and Norris (1978) determined that skeletal muscle mass decreases on average 6% per decade beginning in the 3rd decade. Similarly, Fleg and Lakatta (1988), using creatinine excretion, confirmed that muscle mass decreased between the ages of 30 and 70 years, by 23% and 22%, in men and women, respectively. In addition, Cohn and colleagues (1976), used total body potassium and nitrogen balance to show that the loss of total body protein was almost exclusively due to the loss of skeletal muscle protein, whereas non-muscle protein was maintained with increasing age. This suggested that skeletal muscle protein was especially susceptible to age-related changes.

Muscle cross-sectional area (CSA) and muscle volume have been estimated using various radiological imaging techniques (Young et al., 1984; Rice et al., 1989). Using ultrasonography, Young and colleagues (1984, 1985) reported a reduction of

25-35% in the CSA of the quadriceps muscle in older men and women as compared to younger men and women. Studies using computerized tomography have reported a decrease of 12-16% in thigh CSA and muscle density with a concomitant increase in subcutaneous and intramuscular fat, and infiltration of fat and connective tissue into the muscle in older individuals (Borkan et al., 1983; Frontera et al., 2000). Similar age-associated reductions in CSA have been reported in the biceps and triceps muscles (Rice et al., 1989), and the plantar flexors (Rice et al., 1989). Thus, despite some controversy in the literature with respect to the amount of muscle mass lost with aging, age-related muscle atrophy remains an undisputed finding. Given the well characterized declines in muscle protein mass and muscle contractile function in older adults, several interventions were proposed and evaluated as countermeasures to these phenomenon (Fiatarone et al., 1990, 1994).

1.3 Age Associated Changes in Muscle Morphology

1.3.1 Muscle Fiber Types

Skeletal muscle fibers are classified into different types based on their contractile, physiological, ultrastructural, and metabolic characteristics (Brooke and Kaiser, 1970; Essén et al., 1975). Originally, human skeletal muscle fibers were generally classified as type I (slow-twitch) and type II (fast-twitch), however, using histochemical staining, it was determined that the type II group contains two main subtypes, type IIa and type IIb (Brooke and Kaiser, 1970; Schluter and Fitts, 1994). More recent work has determined that true type IIb fibers probably do not exist in

humans (Pereira Sant'Ana et al., 1997; Smerdu et al., 1994), and these fibers are more accurately characterized as type IIx. Each fiber type has a characteristic profile and is best suited for a particular type of activity. Human skeletal muscle contains varying proportions of both fiber types and is functionally dependent on its fiber composition. A histochemical reaction for myosin ATPase, following acid or alkaline pre-incubations, is used to distinguish between fiber types (Brooke and Kaiser, 1970). Classification using the Brooke and Kaiser (1970) method yields a minimum of the following fiber types: type I, type IIa and type IIx.

1.3.2 Muscle Fiber Size

In humans, decreased muscle mass has commonly been attributed to a decrease in muscle fiber size (Larsson et al., 1978). It has generally been accepted that the size of type II fibers is markedly reduced with advancing age, while the size of type I fibers remains relatively constant (Aniansson et al., 1981, 1986; Grimby et al., 1982; Larsson et al., 1978). Biopsy samples from the *vastus lateralis* muscle of sedentary men (22-65 years) revealed a 33% decrease in absolute type II fiber area in older men (60 to 65 years) as compared to younger men (20 to 29 years) (Larsson et al., 1978). Consequently, the relative type II fiber area decreased by approximately 20% in the older men (60-65 years) (Larsson et al., 1978). Furthermore, Grimby and associates (1982) reported a decline in type II fiber area, especially type IIx, in the *vastus lateralis* muscle of men and women (78-81years) as compared with fiber areas from younger individuals drawn from population studies. Preferential atrophy of type IIx

fibers compared with type IIa fibers in older individuals may suggest that these fibers are more susceptible to the effects of aging (Grimby et al., 1982). Consistent with these findings are those reported by Lexell and colleagues (1988) who reported no significant change in type I muscle fiber size with age; however, a 26% reduction in type II fiber size was observed between the ages of 20 and 80 years.

Few longitudinal studies have assessed the changes in muscle fiber size with age (Aniansson et al., 1986; Frontera et al., 2000). Aniansson and colleagues (1986) reported that type IIa and IIx fiber areas of the *vastus lateralis* decreased by 14% and 25%, respectively, while type I fiber area remained unchanged in men aged 73 to 83 years over a 7 year time span. In contrast to these findings, Frontera and colleagues (2000) reported no change in type I or type II mean fiber areas of the *vastus lateralis* in older men (65.4±4.2 years at baseline) over a 12 year period. The observations by Frontera and colleagues (2000) suggested that muscle atrophy may, at least in part, be explained by a reduction in the number of muscle fibers, rather than a decrease in mean fiber area.

1.3.3 Muscle Fiber Number

Muscle atrophy, in part, has also been attributed to a gradual and selective loss of muscle fibers. Early studies suggested that the reduction in muscle size that occurs with advancing age is due to a reduction in the total number of fibers with no obvious reduction in muscle fiber size (Lexell et al., 1983, 1988). According to an autopsy study, Lexell and colleagues (1983) reported that the number of fibers in the *vastus*

lateralis muscle is reduced by 25% in elderly men (70-73 years) as compared to young men (19-37 years), while the mean fiber size did not change significantly between the age groups. Using a quadratic relationship, Lexell and colleagues (1988) suggested that muscle fiber number begins to decrease at 25 years of age, with the total number of fibers decreasing by 39% by 80 years of age. A similar study examining the *pectoralis minor* muscle of women reported that muscle fiber numbers begin to decrease at 60 years of age, with a 25% reduction in muscle fiber number by the 7th decade (Sato et al., 1984). Thus, from these studies, it has been concluded that age-related muscle atrophy is mainly due to a reduction in the number of muscle fibers and, to a lesser extent, a reduction in type II fiber size.

1.3.4 Fiber Type Distribution

The effect of aging on fiber type distribution remains unclear. Some studies reported no change in fiber type distribution (Essén-Gustavsson and Borges, 1986; Grimby et al., 1984; Lexell et al., 1983; Porter et al., 1995). Others reported an increase in the percentage of type I fibers (Gollnick et al., 1972; Larsson and Karlsson, 1978; Larsson et al., 1978, 1979), while others still, reported a decrease in the percentage of type I fibers (Frontera et al., 2000) with advancing age. Early studies which examined fiber type distribution reported a shift toward a distribution with a higher percentage of type I fibers and a corresponding decrease in type II fibers with advancing age (Gollnick et al., 1972; Larsson, 1982; Larsson and Karlsson, 1978; Larsson et al., 1978). Larsson and colleagues (1978) reported that

the percentage of type I fibers in the *vastus lateralis* muscle in older (60-65 years) and younger (20-29 years) men was 55% and 41%, respectively. A more recent longitudinal study reported an increase in the percentage of type I fibers in the *gastrocnemius* muscle after 20 years, however, the study population consisted of aerobic athletes with a mean age of 47-50 years at follow-up (Trappe et al., 1995).

In contrast to the above findings, Lexell and colleagues (1986) used whole muscle cross-sections to demonstrate no significant alteration in fiber type distribution. Using this technique, they reported that young men (24 years), middle-aged men (52 years), and elderly men (77 years) had 49%, 52%, and 51% type I fibers, respectively (Lexell et al., 1986). Similarly, Grimby and Saltin (1983) used the muscle biopsy technique and reported no age related differences in type I fiber distribution in individuals between 66 and 100 years of age. In addition, Sato and associates (1984) examined the *pectoralis minor* muscle in 200 women between 26 and 80 years of age and found that the percentage of type I fibers did not change with age. Thus, these results suggested that the loss of muscle mass with aging was not due to the preferential loss of a specific fiber type or alteration in fiber type distribution.

1.3.5 Denervation and Muscle Fiber Loss

Studies using electromyography (EMG) have reported that the number of excitable motor units decreases beginning in the 7th decade (Doherty et al., 1993; McComas et al., 1973) and that the remaining low threshold motor units in older

individuals become progressively larger by capturing neighbouring fibers of failing motoneurons (Sperling, 1980). In addition, older muscles displayed an increase in fiber-type grouping and preferential atrophy of type II fibers which has been interpreted as evidence for a denervation and reinnervation model (Lexell and Downham, 1991). Lexell and Downham (1991) assessed fiber type grouping in whole *vastus lateralis* muscle cross-sections in men between the ages of 15 and 83 years of age and found that segregated fibers were common in young muscles, a random mosaic-like pattern predominated in men between the ages of 30 and 50 years, and over 60 years an excess of enclosed fibers were evident. The observed fiber type grouping implies that the fiber population is continually in a state of transition throughout life and that denervation and reinnervation occur in normal muscle during aging.

In summary, the age-associated loss of muscle mass is partially due to a reduction in the size of type II fibers (Anniansson et al., 1981, 1986; Grimby et al., 1982; Larsson et al., 1978, 1979) and an overall loss of type I and type II muscle fibers (Lexell et al., 1983, 1988). It is thought that the age-associated changes in muscle fiber area and number are due to a combination of factors, including, motor unit dropout, a denervation and reinnervation process and physical inactivity.

1.4 Age Associated Changes in Muscle Protein Synthesis

The loss of muscle mass that occurs with aging is, in part, due to an imbalance between the rates of muscle protein synthesis and muscle protein breakdown. The rate

of mixed skeletal muscle protein synthesis is reduced in older men and women as compared to younger men and women (Yarasheski et al., 1993). Moreover, a decrease in the fractional synthetic rate (FSR) of individual muscle proteins has also been reported in older adults (Balagopal et al., 1997; Welle et al., 1993). Balagopal and colleagues (1997) have shown that myosin heavy chain synthesis is decreased with advancing age. Similarly, Welle and colleagues (1993) reported that the fractional synthetic rate of myofibrillar protein was approximately 30% lower in older adults (60 to 70 years) as compared with younger adults (<35 years). Taken together, it appears that a decreased rate of skeletal muscle protein synthesis and myofibrillar protein synthesis in older adults contributes to the loss of muscle mass and may be an important mechanism associated with muscle atrophy in older adults.

Resistance exercise has been implicated in increasing protein synthesis and preventing protein breakdown in older adults (Welle et al., 1995; Yarasheski et al., 1993, 1995). Yarasheski and colleagues (1993) reported a similar increase in mixed and myosin heavy chain protein synthesis in both younger and older adults following 2 weeks of whole body resistance exercise training. Furthermore, whole body protein breakdown rate did not change. The stimulation of acute muscle protein synthesis in older adults appears to be mediated by post-transcriptional events (Welle et al., 1999). Welle and colleagues (1999) reported a 30% increase in myofibrillar protein synthesis rate following 3 bouts of resistance exercise with no increase in total RNA, actin or myosin heavy chain mRNA. Taken together, the above results suggest that older adults preserve the ability to stimulate processes responsible for skeletal muscle

protein synthesis (Welle et al., 1999; Yarasheski et al., 1993). These findings justify the use of resistance exercise as a countermeasure and potential therapy during old age to prevent the loss of muscle mass and strength.

1.5 Age Associated Changes in Hormone Levels

Several hormones have been identified as having anabolic effects with respect to muscle mass including, testosterone, estrogen, dehydroepiandrosterone (DHEA), and growth hormone (GH). Aging is associated with a reduction in circulating contents of these hormones, and thus, withdrawal of their trophic effects may lead to muscle atrophy and sarcopenia.

1.5.1 Testosterone and Estrogen

Testosterone is a naturally occurring steroid that is synthesized primarily by the Leydig cells of the testis and also in the adrenal cortex. Aging is accompanied by decreased serum total and free testosterone levels in healthy men (Morley et al., 1997). Between the ages of 25 and 75 years, mean serum and free testosterone levels have been reported to decline by 30% and 50%, respectively (Morley et al., 1997). Testosterone is known to induce muscle hypertrophy through stimulation of protein synthesis, thus, it is reasonable to suggest that an age-related decrease in testosterone concentration in men and women may contribute to concomitant changes in body composition (ie. a reduction in muscle mass and an increase and redistribution of body fat).

The most convincing evidence for a role of testosterone in age-related sarcopenia was found in studies which have examined the effects of testosterone supplementation in healthy older men (Sih et al., 1997; Urban et al., 1995) and hypogonadal men (Bhasin et al., 1997; Brodsky et al., 1996). Intramuscular testosterone enanthate injection (100 mg/week) to hypogonadal men (19 to 47 years) for 10 weeks increased bench press and squat strength by 22% and 44%, respectively (Bhasin et al., 1997). In addition, there was a significant increase in TBM (4.5 kg), FFM (5.0 kg), triceps arm muscle CSA (12%) and quadriceps leg muscle CSA (8%) following testosterone supplementation (Bhasin et al., 1997). These results demonstrate that testosterone has substantial effects on body composition. Interestingly, muscle size and strength increased significantly despite the lack of resistance exercise training. Testosterone administration (200 mg every 2 weeks for 12 months) has been shown to increase mid arm circumference and grip strength in healthy older men between 51 and 79 years of age (Sih et al., 1997). Similarly, testosterone administration in older men has been shown to increase leg muscle strength after only 1 month of treatment (Urban et al., 1995). The increased FFM and muscle strength may in part be explained by an effect of testosterone on muscle protein synthesis. Bimonthly administration of testosterone (3mg/kg for 6 months) to hypogonadal men resulted in a 15% increase in FFM and a similar decrease in fat mass (11%) (Brodsky et al., 1996). The changes in body composition were accompanied by a 56% increase in the FSR of mixed skeletal muscle protein and a 46% increase in the FSR of myosin heavy chain (Brodsky et al., 1996). Similarily,

Ferrando and colleagues (1998) and Urban and colleagues (1995) reported that testosterone administration resulted in a stimulation of mixed muscle protein FSR. Finally, Ferrando and colleagues (1998) demonstrated that mixed muscle protein fractional breakdown rate (FBR) was unchanged following acute testosterone administration (200 mg). These studies suggest that testosterone replacement therapy may improve muscle strength and promote a positive protein balance in older men; however, the possible side effects (i.e. prostate cancer) testosterone administration are unknown therefore testosterone replacement therapy should be monitored closely. In addition, it remains to be determined whether testosterone replacement therapy can improve the quality of life and reduce the number of falls in healthy older men.

In women, the decline in estrogen has been well documented during menopause. Few studies, however, have examined the loss of muscle mass during the menopausal years (Aloia et al. 1991; Poehlman et al., 1995). Poehlman and colleagues (1995) observed a decrease in FFM with a corresponding increase in fat mass and drop in metabolic rate during 6 years of follow-up in women who were pre-menopausal at baseline and post-menopausal at the conclusion of the study. This may suggest that acute changes in estrogen availability may play a role in the alteration of body composition during the menopausal years. Furthermore, Phillips and colleagues (1993) observed that hormone replacement therapy (HRT) prevented the loss of specific force in post-menopausal women. In addition, women of the same age on HRT were significantly stronger as compared to those not on HRT, and specific force of pre-menopausal women was not different from that of post- or peri-menopausal

women on HRT. Based on these findings declines in estrogen experienced during menopause may be one cause of age-associated muscle loss in women.

1.5.2 Growth hormone and insulin like growth factor-1

The growth hormone/insulin like growth factor-1 (GH/IGF-1) axis may also contribute to age-associated sarcopenia. GH is secreted from the anterior pituitary in a pulsatile fashion making it difficult to measure the 24-hour secretion of the hormone. The secretion of GH is modulated by several signals from the periphery, including IGF-1. The number and amplitude of GH secretory bursts progressively declines commencing in the 4th decade in both men and women (Zadik et al., 1985) and parallels the decline in lean body mass. Approximately 50% of people over the age of 65 have been reported to be partially or totally GH deficient, which may contribute to impaired muscle function (Rudman et al., 1990).

IGF-1 is produced and released by the liver in response to GH and is stable in plasma (Clemmons and Van Wyk, 1984). Circulating IGF-1 concentration is decreased in elderly men and women, as a consequence of reduced GH secretion (Corpas et al., 1993). Circulating IGF-1 concentration in the 7th decade of life is approximately half of that in the 3rd decade (Corpas et al., 1993), suggesting an age-related reduction which coincides with reductions in FFM.

The functional consequences of a decline in GH secretion and IGF-1 levels remain unclear. Recently, several studies have examined GH treatment in healthy older adults. In general, beneficial effects on body composition and muscle strength

have been reported, suggesting that long term trials are worth serious consideration (Holloway et al., 1994; Rudman et al., 1990; Welle et al., 1996). In addition, IGF-1 administration has been shown to increase whole body protein synthesis and breakdown (Thompson et al., 1995). However, the benefits and safety of GH and IGF-1 administration must be further addressed before GH and IGF-1 can be considered for treatment of sarcopenia.

1.5.3 Dehydroepiandrosterone

Dehydroepiandrosterone (DHEA) and its sulfate (DHEAS) are multifunctional steroid precursors produced by the adrenal cortex. DHEA is the most abundant circulating steroid and is the most active form of the two. Circulating concentrations of DHEA and DHEAS in humans increase progressively beginning at about 5 to7 years of age, peak in the 3rd decade of life, and decline shortly thereafter by an average of about 10% per decade (Orentreich et al., 1984). The rate of decrease is accelerated after the 8th decade of life (Birkenhager-Gillesse, 1994). The decline in DHEA and DHEAS parallels the decline of the GH/IGF-1 system (Orentreich et al., 1984), which suggests a potential link between DHEA and other anabolic pathways thought to be implicated with advancing age.

CONSEQUENCES OF AGING

1.6 Loss of Muscle Strength

Reductions in muscle strength and maximal force production are a common consequence of normal aging (Grimby and Saltin, 1983; Larsson et al., 1979; Larsson and Karlsson, 1978). In a classic study by Larsson and colleagues (1979), maximal isometric and dynamic strength of the quadriceps increased up to 30 years of age, remained constant until 50 years of age, and then decreased by 15% per decade between the ages of 50 and 70 years. A loss of muscle strength is more profound after 70 years of age, accelerating to a loss of approximately 30% per decade (Danneskoild-Samsoe et al., 1984). The decline in muscle strength was similar in magnitude to the decline in muscle mass over the same age range. Therefore, it is thought that a decline in muscle mass is a contributing factor to the loss of muscle strength that occurs with age.

In a cross-sectional study, Klitgaard and colleagues (1990) reported that maximum voluntary isometric torque production of the knee extensors and elbow flexors was 44% and 32% lower in older men (69±1 years), than in younger men (28±1 years). Similarly, older women (70 years) had 35% lower maximal voluntary isometric muscle strength of the quadriceps as compared to younger women (20 years) (Harries and Bassey, 1990; Young et al., 1984).

Longitudinal studies have also reported a loss in muscle strength in older men and women (Aniansson et al., 1986; Frontera et al., 2000; Hughes et al., 2001; Winegard et al., 1996). Bassey and Harries (1993) reported a reduction of 12% and

19% in hand-grip strength in men and women over 65 years of age over a 4 year time period. Strength losses ranging from 9-27% after five years (Aniansson et al., 1983), 10-22% after seven years (Aniansson et al., 1986), and 25-35% after 11 years (Aniansson et al., 1992) have been demonstrated in the *vastus lateralis* of elderly men. In a recent 12 year longitudinal study, Frontera and colleagues (2000) measured isokinetic strength of the knee and elbow extensors and flexors at slow and fast angular velocities in healthy older men (65.4±4.2 years) measured on two occasions 12 years apart. Knee extensor and flexor strength decreased at an average rate of 2.0% and 2.5% per year, respectively. Similarly, elbow flexor and extensor strength decreased at an average rate of 1.6 and 2.2% per year, respectively. In addition, muscle cross-sectional area (measured using computerized tomography) decreased in the thigh (-12.5%), all thigh muscles (-14.7%), quadriceps femoris muscle (-16.1%), and flexor muscles (-14.9%). In summary, both longitudinal and cross-sectional studies consistently show an age-related decline in muscle strength. Longitudinal studies appear to demonstrate that changes in dynamic muscle strength over time can be as much as 60% greater than that measured in cross-sectional studies, perhaps related to genetic potential and other factors not controlled for in cross-sectional studies.

More recently, a loss in muscle quality has been reported to contribute to the age-associated loss in strength (Lynch et al., 1999; Welle et al., 1996). Lynch and colleagues (1999) reported a linear age-related decline in leg and arm muscle quality measured in 703 men and women (19 to 93 years). These observations indicate that

the loss of muscle strength and mass with advancing age involve more than a loss of muscle protein mass. In support of this finding, recent work has shown that muscle quality measured at the single fiber level decreased with age (Frontera et al., 2000). Single type I and IIa fibers were stronger in younger men as compared to older men, even after correcting for fiber size, indicating that contractile protein may become defective with age.

1.7 Decline in Functional Ability

The loss of muscle protein and strength in the elderly is closely associated with the ability to perform functional activities of daily living. Impairment in muscle strength, especially leg weakness, results in a progressive loss of physical function, limits recreational activity, increases dependency on others, leads to disability and frailty, and contributes to a decrease in self-worth (Bassey et al., 1992; Buchner and DeLateur, 1991; Rantanen et al., 1998). In addition, decreased lower body strength is associated with an increased incidence of falls in both non-institutionalized and institutionalized older individuals (Province et al., 1995; Whipple et al., 1987).

Decrements in performance on functional tasks in healthy older adults has been attributed to a decrease in muscle strength and power (Bassey et al., 1988, 1992). More specifically, lower extremity strength loss has been associated with an increased time to rise from a chair and climb stairs, and with a decrease in walking speed (Bassey et al., 1988, 1992). Bassey and colleagues (1988) reported a significant negative relationship between quadriceps muscle strength and walking speed in men

and women over 65 years of age. In addition, Bassey and colleagues (1992) observed a significant relationship between leg extensor power and rising from a chair, climbing stairs, and walking speed. These findings suggest that physical disability is prevalent in a large segment of the population over the age of 65 years, and is strongly correlated to muscle strength and function.

1.8 RESISTANCE TRAINING IN THE ELDERLY

Resistance training is defined as training in which the resistance against which muscle generates force is progressively increased over time. Over the past decade, several studies have examined the effects of resistance training as a method of developing muscular strength and maintaining lean body mass in the elderly (Charette et al., 1991; Fiatarone et al., 1990; Frontera et al., 1988). Recently, the ability of strength training to improve performance on functional tasks such as walking, climbing stairs, and rising from a chair have also been examined (Hunter et al., 1995; Schlicht et al., 2001). Muscle hypertrophy, increased muscle strength, alterations in body composition, and improved functional ability have all been documented following resistance training in healthy, community-dwelling older persons. Moreover, many studies have shown that given an adequate training stimulus, older men (Frontera et al., 1988) and women (Charette et al., 1991) demonstrate similar strength gains when compared to young individuals (Kraemer et al., 1998).

1.8.1 Effects on Strength

High intensity resistance training (>70% of 1RM) in older men (Frontera et al., 1988) and women (Charette et al., 1991) has been shown to significantly increase strength, as measured by 1 RM (Table 1). The increases in strength reported in the literature are variable, and have been attributed to improved neuromuscular recruitment efficiency (Moritani and DeVries, 1979), as well as, muscle fiber hypertrophy (Brown et al., 1990; Frontera et al., 1988; Charette et al., 1991).

Frontera and colleagues (1988) examined the effects of a high intensity resistance training program in healthy older men between 60 and 72 years of age. They reported an increase of 107% and 227% in knee extension and knee flexion 1RM strength, respectively, following 12 weeks of high intensity resistance training at 80% of 1RM. This was the first study to demonstrate that healthy older men have the capability to significantly improve muscle strength in response to dynamic high intensity strength training. Similarly, Charette and colleagues (1991) reported that following 12 weeks of resistance training at 80% of 1RM, older women (64-86 years) increased 115%, 93%, and 28% in leg curl, leg extension, and leg press, respectively. From the above studies and those listed in table 1, it can be concluded that muscles in older men and women have the potential to increase strength in response to high-intensity resistance training.

Table 1. Improvements in muscle strength following high intensity resistance training in older individuals.

Authors	Sex	Age	Duration	Muscle Group	% ↑ in 1 RM
Frontera et al., 1988	M	60-72	12 weeks, 3d/wk	Knee Flexion Knee Extension	227% 107%
Brown et al., 1990	M	60-70	12 weeks, 3d/wk	Elbow Flexion	48%
Fiatarone et al., 1990	M/F	86-96	8 weeks, 3d/wk	Knee Extension	174%
Charette et al., 1991	F	64-86	12 weeks, 3d/wk	Leg Flexion Leg Extension Leg Press	115% 93% 28%
Pyka et al., 1994	M/F	61-78	15 weeks, 3d/wk	Leg Flexion Leg Extension Leg Press Bench Press	39% 42% 24% 22%
Roth et al., 1999	M	65-75	9 weeks, 3d/wk	Leg Extension	26%
Hikida et al., 2000	M	58-78	16 weeks, 2d/wk	Leg Extension Leg Press	50% 72%
Ivey et al., 2000	M/F	65-75	9 weeks, 3d/wk	Knee Extension	26%
Roth et al., 2000	F	65-75	9weeks, 3d/wk	Knee Extension	22%

1.8.2 Effects on Body Composition

Previous studies involving the elderly have reported both an increase FFM (Hunter et al., 2000; Taaffe et al., 1999; Treuth et al., 1994) and no change in FFM (Ades et al., 1996; Bermon et al., 1998) following resistance exercise training. The lack of consistent findings in these studies may be influenced by the intensity and duration of exercise, as well as the precision of measurement. In addition, most of these studies involved male subjects. Studies reporting no change in FFM following resistance training have often used anthropometry (Bermon et al., 1998) and hydrodensitometry (Ades et al., 1996) to estimate muscle mass. It is possible that these techniques are not sensitive enough to detect subtle changes in body composition following resistance training (Lohman, 1981). In contrast, studies using

more sensitive measures to determine body composition such as dual-energy X-ray absorptiometry (DEXA) (Nichols et al., 1993; Taaffe et al., 1999; Treuth et al., 1994), magnetic resonance imaging (Hurley et al., 1991), and computerized tomography (Brown et al., 1990; Fiatarone et al., 1990; Frontera et al., 1988), have consistently reported an increase in FFM or an increase in muscle CSA following resistance training exercise. Inherent in all of these techniques are limitations, particularly with older subjects, that may make inferences about whole body mass changes ambiguous (Lee et al., 2001).

Treuth and colleagues (1994) examined the effects of strength training on total and regional body composition in older men between the ages of 51 and 71 years. The resistance training program consisted of 14 exercises which were performed 3d/wk for 16 weeks. FFM increased by 2 kg, and fat mass decreased by the same extent, as measured by DEXA. Furthermore, fat mass in the arms and legs decreased significantly with training, whereas FFM in the arms and legs increased significantly with training. Similarly, Hunter and colleagues (2000) reported that 26 weeks of strength training significantly decreased body fat by 3.4% and fat mass by 3.1 kg, and significantly increased FFM by 2 kg in healthy older men and women (61 to 77 years).

Measurements of site specific muscle hypertrophy following resistance training have also been made using computerized tomography (Brown et al., 1990; Fiatarone et al., 1990; Frontera et al., 1988) and magnetic resonance imaging (Hurley et al., 1991). Frontera and colleagues (1988) reported a 9% increase in the CSA of the

quadriceps muscle and an 11% increase in total thigh area, as measured by computerized tomography, following 12 weeks of high intensity resistance training in elderly men (60 to 72 years). Similarly, Fiatarone and colleagues (1990) reported an increase in mid-thigh muscle area (9%) and total muscle area (15%) following 8 weeks of strength training in frail elderly men and women (86 to 96 years). Furthermore, Brown and associates (1990) reported a 17% increase in the CSA of the elbow flexors following 12 weeks of resistance training in elderly men (60 to 70 years). Therefore, resistance training in older adults resulted in increased muscle CSA in both upper and lower extremities.

1.8.3 Effects on Muscle Morphology

Considerable evidence has indicated that resistance training results in skeletal muscle hypertrophy, which leads to increased maximum force generating capacity and power development. An increase in the muscle fiber area of type I, type IIa, and type IIx fibers has been demonstrated following short-term high intensity training in older adults (Table 2; Brown et al., 1990; Charette et al., 1991; Frontera et al., 1988; Hagerman et al., 2000; Hikida et al., 2000; Pyka et al., 1994). Frontera and colleagues (1988) reported a 33% and 27% increase in type I and type II fiber area following 12 weeks of knee flexor and extensor training for 3d/week at 80% of 1RM in elderly men. Subsequently, a study by Charette and colleagues (1991) confirmed that dynamic resistance training in healthy elderly women also resulted in a significant increase in type II muscle fiber area following training. However, in

contrast to findings of Frontera and associates (1988), there was no change in type I fiber area following training. These discrepancies may be related to the initial pre-training activity patterns of the various subject populations. The observed increase in muscle fiber area supports the conclusion that skeletal muscle of older men and women retains the capacity to undergo hypertrophy.

Table 2. Increases in muscle fiber size following high-intensity, dynamic strength training in older adults.

Authors	Sex	Age	Duration	Muscle Fiber Size Increase	
				Type I	Type II
Frontera et al., 1988	M	60-72	12 weeks, 3d/wk	34%	28%
Brown et al., 1990	M	60-70	12 weeks, 3d/wk	14%	30%
Charette et al., 1991	F	64-86	12 weeks, 3d/wk	7%	20%
Pyka et al., 1994	M/F	61-78	15 weeks, 3d/wk	25%	20%
Ferketich et al., 1998	W	60-75	12 weeks, 3d/wk	20%	22%
Häkkinen et al., 1998	M	61±4	10 weeks, 3d/wk	23%	Type IIa – 39% Type IIx – 19%
Campbell et al., 1999	M	51-69	9 weeks, 2d/wk	2%	16%
Hikida et al., 2000	M	58-78	16 weeks, 2d/wk	46%	Type IIa - 34% Type IIx - 52%

1.8.4 Effects on Functional Capacity

Current evidence has suggested that healthy older individuals respond favorably to strength training interventions. With an increasing proportion of older adults in society, it is important that functional ability is improved as a result of exercise training. However, there are few studies that have examined the effect of resistance training on functional tasks, such as walking speed, climbing up and down stairs, and sit-to-stand performance (Fiatarone et al., 1994; Hunter et al., 1995; Schlicht et al., 2001).

Recent studies have demonstrated that progressive resistance training in older adults resulted in marked increases in functional capacity. Fiatarone and colleagues (1990) examined 10 frail elderly men and women (86-96 years) who performed knee extension exercise 3d/week at 80% of 1RM for 8 weeks. Following 8 weeks of training a 48% increase in tandem gait speed was observed. Subsequently, Fiatarone and colleagues (1994) examined the functional benefits of 10 weeks of resistance exercise in older men (n=37) and women (n=63) between 72 and 98 years of age. Lower body resistance exercise training resulted in increased muscle strength (113%), gait velocity (12%), and stair-climbing power (28%). In a more recent study, Schilcht and colleagues (2001) reported a 17% increase in walking speed and a 15% decrease in 5-repetition sit-to-stand timed test in subjects (61-87 years) after 8 weeks of resistance training. In general, these studies suggest that an increase in muscle strength is correlated with improvements in activities of daily living and physical activity which ultimately contribute to greater well-being.

In summary, resistance exercise training is an effective, non-pharmacological intervention that can be used to offset the negative consequences of aging by minimizing age-associated losses in muscle strength, muscle mass, and functional performance (Charette et al., 1991; Fiatarone et al., 1990; Frontera et al., 1988). The adaptations in aging skeletal muscle to resistance exercise training may prevent or attenuate the age-associated changes in skeletal muscle, thereby increasing the ability of older adults to perform activities of daily living and improve the quality of life in older adults.

CHAPTER 2: Creatine

2.1 Creatine Synthesis

Creatine is a guanidino compound found in food sources such as meat and fish, and is produced endogenously by the liver, kidney, and pancreas. Creatine is synthesized enzymatically from arginine, glycine, and methionine (Bloch and Schoenheimer, 1941). Creatine synthesis begins with the transfer of the amidine group from arginine to glycine resulting in the formation of guanidinoacetate and L-ornithine. This reaction is catalyzed by the enzyme L-arginine:glycine amidinotransferase (AGAT). The addition of a methyl group from S-adenosylmethionine to guanidinoacetate results in the formation of creatine. This irreversible reaction requires the enzyme S- adenosylmethionine:guanidinoacetate methyltransferase (GAMT) (Figure 1; Bloch and Schoenheimer, 1941; Guthmiller et al., 1994; Walker, 1979).

2.2 Creatine Transport and Storage

Since creatine is exclusively produced in the liver, kidney, and pancreas, and 90-95% of creatine is found in skeletal muscle, it stands to reason that creatine must be transported from the blood stream into skeletal muscle. Creatine enters skeletal muscle, against a concentration gradient, via a sodium and chlorine dependent creatine transporter (CreaT) located in the sarcolemma (Guimbal et al., 1993); however, very little is known about its expression and cellular localization.

The total creatine pool in an average 70-kg male amounts to ~120 grams with approximately 95% of the total pool located in skeletal muscle. The remaining 5% is found in cardiac muscle, brain, testes, and other organs (Walliman and Hemmer, 1994). Total creatine (TCr) is the sum of free creatine (Cr_f) and phosphocreatine (PCr). TCr concentration in skeletal muscle is approximately 125 mmol/kg dry mass, but it can vary widely among individuals (90 to 190 mmol/kg dry mass) (Green et al., 1996; Greenhaff, 1995; Harris et al., 1992). PCr accounts for 60% of the total creatine, while Cr_f accounts for the remaining 40% (Harris et al., 1992; Hultman et al., 1996), and both can be spontaneously converted to creatinine (Crn) and excreted in the urine at a rate of ~2g/d (~ 1.7%/d). Urinary excretion of Crn will vary as a function of muscle mass. Thus, Crn excretion, on average, is less in woman than men and less in the elderly than the young (Tzankoff and Norris, 1978).

2.3 Roles of the Creatine Kinase/Phosphocreatine System

2.3.1 Temporal Energy Buffer

The creatine kinase/phosphocreatine (CK/PCr) system has been suggested to serve as a temporal energy buffer, preventing the accumulation of adenosine diphosphate (ADP) in the cytosol. Furthermore, this system also buffers H^+ ions in the cytosol to prevent intracellular acidosis. PCr is a high-energy phosphorylated compound that provides a reserve of phosphate energy to regenerate adenosine triphosphate (ATP) that is utilized during muscle contraction. In order to maintain

muscle contraction, ATP must be rapidly regenerated. The interaction of PCr and ADP is catalyzed by the enzyme creatine kinase (CK) in the following reaction,

$$PCr + ADP + H^{+} \longrightarrow ATP + Cr.$$

The above reaction can produce ATP for 10-20 seconds of maximal, anaerobic exercise, after which other systems are required for ATP production (Hultman et al., 1991). Creatine supplementation may influence the temporal component of the CK/PCR system by: 1) increasing the initial storage of intramuscular PCr (Casey et al., 1996; Harris et al., 1992; Hultman et al., 1996); and 2) increasing the resynthesis of PCr during recovery periods after intense exercise (Greenhaff et al., 1994).

2.3.2 Spatial Energy Buffer

More recently, it has been proposed that the CK/PCr system acts as a 'spatial energy buffer' or 'energy transport' system (Wallimann et al., 1992; Wyss and Wallimann, 1994). CK exists in different isoforms which are compartmentalized in either the cytosol (cCK) or the mitochondria (mtCK). This enzyme catalyzes the reversible transfer of a phosphate group from PCr to ADP, allowing the regeneration of ATP (Figure 2). The different isoforms of CK connect sites of energy production (glycolysis and oxidative phosphorylation) to sites of energy utilization (myofibrils and ion pumps).

During muscle contraction, ATP is hydrolyzed to ADP which is then rephosphorylated by PCr via the enzyme cCK. The resulting Cr_f is transported through porin into the intermitochondrial space where it is rephosphorylated by ATP

via the enzyme mtCK. The resulting PCr leaves the intermitochondrial space via porin and returns to the cytosol where it can be used to resynthesize ATP. Simultaneously, ATP is being produced in the mitochondria by the electron transport chain (ETC). ATP is transported from the mitochondrial matrix, through the inner mitochondrial membrane to the intermitochondrial space by the adenine nucleotide translocase (ANT) in exchange for ADP. In summary, it is believed that PCr acts as an 'energy carrier', transporting mitochondrial derived ATP to sites of energy utilization in the cytosol (Wallimann et al., 1992; Wyss and Wallimann, 1994).

2.4 Creatine and Fiber Type

Skeletal muscle is composed primarily of two major fiber types: slow twitch and fast twitch fibers. Slow twitch fibers (type I) are characterized by high mitochondrial density, high oxidative enzyme capacity, and low myosin ATPase activity and play a role in aerobic energy production. In contrast, fast twitch fibers (type II) are characterized by low mitochondrial density, high glycolytic enzyme activity, high creatine kinase activity and high myosin ATPase activity and play a role in anaerobic energy production (Essén et al., 1975). Measurements on individual human skeletal muscle fibers have revealed that the resting PCr content is approximately 15% higher in type II fibers as compared to type I fibers (Casey et al., 1996; Greenhaff et al, 1994; Söderlund et al., 1991; Tesch et al., 1989). Similarly, fast glycolytic muscles in rats and guinea pigs were shown to have higher PCr and TCr than slow oxidative fibers (Edström et al., 1982). PCr degradation during maximal intensity dynamic

exercise (Greenhaff et al., 1994; Tesch et al., 1989) and electrically evoked isometric contraction (Söderlund et al., 1992) is greater in type II fibers as compared to type I fibers. Type I fibers, however, have a greater ATP resynthesis capability due to their increased mitochondrial density and increased capillary supply (Tesch et al., 1989). After creatine supplementation, TCr and PCr has been shown to increase in both type I and type II fibers, with a trend toward a larger increase in type II fibers (Casey et al., 1996).

2.5 Creatine Supplementation

Several studies have shown that creatine supplementation of 20 g/d for 5 days can increase the TCr in human skeletal muscle by up to 20-25% (Balsom et al., 1995; Casey et al., 1996; Greenhaff et al., 1994; Harris et al., 1992; Hultman et al., 1996; Vandenberghe et al., 1996). Harris and colleagues (1992) were the first to demonstrate that consumption of 5 g of creatine monohydrate (CrM), four or six times a day for 2 or more days resulted in an increased TCr concentration in human skeletal muscle. On average, intramuscular TCr increased from 126.8 to 148.6 mmol/kg dry mass and PCr increased from 84.2 to 90.6 mmol/kg dry mass. The observed increases were highly variable between subjects and were greatest in those with the lowest initial TCr concentration. In other words, the extent of creatine uptake was inversely related to the initial intramuscular TCr content prior to creatine supplementation. Conversely, the higher the initial intramuscular TCr content, the less chance there was for an individual to increase TCr. More recently, Hultman and

colleagues (1996) reported that two dose protocols (20 g/day for 6 days and 3 g/day for 28 days) resulted in similar increases in TCr content.

In addition, Harris and colleagues (1992) have demonstrated that intramuscular TCr concentration can be increased by approximately 37% when submaximal exercise is performed after creatine ingestion. Thus, exercise may further augment the local uptake of creatine into muscle. The authors suggested that increased blood flow in the exercising leg may increase creatine uptake as compared to the control leg (Harris et al., 1992). It has also been reported that muscle creatine retention can be further augmented by 60% by ingesting creatine in combination with high doses (370 g) of simple carbohydrate (Green et al., 1996). These authors suggested that the increase in creatine retention observed after carbohydrate and creatine ingestion may be due to a stimulatory effect of insulin on muscle creatine transport (Green et al., 1996). More recently, it has been demonstrated that insulin increases intramuscular creatine retention in individuals when insulin is present at a concentration ≥ 100mU/l (Steenge et al., 1998). Furthermore, Steenge and colleagues (2000) reported that creatine retention can be augmented by ~25% in individuals consuming a protein-carbohydrate mixture in conjunction with creatine. Thus, it has been proposed that ingestion of creatine with smaller doses of carbohydrate combined with protein may also optimize creatine accumulation.

2.6 Creatine Supplementation and Performance

Short-term creatine supplementation has been shown to increase muscle force (Earnest et al., 1995; Maganaris and Maughan, 1998), and improve power output during short bouts of high-intensity intermittent exercise (Balsom et al., 1993; Birch et al., 1994; Casey et al., 1996; Greenhaff et al., 1993; Harris et al., 1992; Tarnopolsky and MacLennan, 2000) in healthy, young men. The greatest improvements in performance seem to be observed during repetitive exercise bouts with performance in the latter bouts increasing by 5-20% (Balsom et al., 1993, 1995; Birch et al., 1994; Greenhaff et al., 1993).

2.7 Creatine Supplementation and Body Composition

Many studies have reported an increase in total body mass (TBM) (Balsom et al., 1993; Kraemer and Volek, 1999; Volek et al., 1997) and FFM (Mihic et al., 2000) following short-term creatine supplementation. However, the underlying mechanisms responsible for the increase in body mass remains to be elucidated. The observed increase in TBM may be the result of an increased water retention which would change the relative volume of the intracellular compartment (Hultman et al., 1996). Furthermore, 3 days of creatine supplementation has been reported to increase intracellular fluid volume measured using multi-frequency bio-electric impedance (Ziegenfuss et al., 1998). It has also been shown that creatine supplementation can increase muscle glycogen synthesis and storage in man, thus, water bound to

glycogen is likely to account for some of the increase in TBM following creatine supplementation (Op't Eijnde B et al., 2001). Therefore, it is reasonable to suggest that the rapid onset of weight gain following short-term creatine supplementation is likely due to fluid retention.

Long term creatine supplementation has also been shown to increase TBM and FFM in young men (Kreider et al., 1998; Tarnopolsky et al., 2001; Volek et al., 1999) and women (Vandenberghe et al., 1997). Thus, it has also been suggested that the increase in TBM and FFM may be in part due to a stimulation of protein synthesis leading to an increase in muscle protein accretion (Ingwall, 1976; Ingwall et al., 1974). Ingwall (1976) observed that the addition of creatine to incubated embryonic muscle cells *in vitro* resulted in enhanced myofibrillar protein synthesis. In contrast, Fry and Morales (1980) did not find that creatine stimulated total protein of myosin heavy chain synthesis in cell culture. It should be noted, however, that *in vitro* studies examining cells which are either completely creatine deficient or sufficient are not representative of *in vivo* physiology (Fry and Morales, 1980; Ingwall, 1976) . Chronic creatine supplementation in humans has provided indirect evidence that creatine may potentially enhance net protein balance (Sipilä et al., 1981; Volek et al., 1999). Sipilä and colleagues (1981) observed an increase in type II muscle fiber diameter (46%) and improved strength in patients with gyrate atrophy who were administered creatine (1.5 g/d) for 1 year. Furthermore, after the cessation of creatine supplementation, type II fiber atrophy was again documented (Vannas-Sulonen et al., 1985). Recently, Volek and colleagues (1999) reported that the muscle fiber area of

all three fiber types increased significantly following resistance training combined with CrM supplementation. In contrast, Tarnopolsky and colleagues (2001) reported that muscle fiber area increased similarly following resistance training for individuals receiving either a creatine-carbohydrate (CrM-CHO) or a protein-carbohydrate (PRO-CHO) supplement (Tarnopolsky et al., 2001). From the above studies, it cannot be determined to what extent the increases in FFM and TBM are due to water retention or to an altered protein metabolism. Therefore, further experiments are needed to elucidate the link between creatine supplementation and increased TBM and FFM.

2.8 Creatine Supplementation and Resistance Training

A few studies have examined the combined effects of creatine supplementation and resistance training (Bermon et al., 1998; Earnest et al., 1995; Kreider et al., 1998; Tarnopolsky et al., 2001; Vandenberghe et al., 1997; Volek et al., 1999). An early study by Earnest and associates (1995) examined the influence of creatine supplementation on muscular power and strength indices in 10 experienced weightlifters. They reported a 26% increase in total lifting volume and a 1.7 kg increase in body weight in the group supplemented with creatine as compared to placebo. Vandenberghe and colleagues (1997) investigated the influence of resistance training in conjunction with creatine supplementation in young untrained females (19-22 years) for 10 weeks. Compared with placebo, 1 RM muscular strength increased 20-25% more for the leg press, leg extension, and squat exercise following CrM supplementation. Also, FFM, measured by densitometry, increased

significantly more (2.6 kg) in the CrM group as compared to placebo (1.6 kg). Similarly Kreider and colleagues (1998) confirmed that CrM supplementation resulted in a greater increase in TBM, FFM, and functional capacity as compared to placebo in young men following 4 weeks of resistance exercise training. In addition, Volek and colleagues (1999) reported a greater increase in TBM and FFM in individuals supplemented with CrM (6.3% and 6.3%, respectively) as compared to placebo (3.6% and 3.1%, respectively). Lastly, Tarnopolsky and colleagues (2001) reported a greater increase in TBM for the CrM-CHO group (4.3 kg) as compared to PRO-CHO group; however, the increase in FFM was similar for both groups. In summary, studies examining the effects of creatine supplementation in conjunction with resistance training have reported gains in TBM, FFM, muscular strength and total lifting volume in both men (Earnest et al., 1995; Kreider et al., 1998; Volek et al., 1999) and women (Vandenberghe et al., 1997). Only two of these studies, however, have measured intramuscular TCr and changes in skeletal muscle morphology (Tarnopolsky et al., 2001; Volek et al., 1999). Future studies should examine the influence of creatine supplementation and resistance training on skeletal muscle morphology and intramuscular PCR, Cr_f and TCr concentrations. Moreover, the increase in FFM due to chronic creatine supplementation may reduce muscle atrophy observed in aging and various disease conditions. Therefore, future studies should continue to investigate the effect of oral creatine supplementation on cross-sectional area, muscle strength and functional capacity in these populations.

2.9 Potential Side Effects

There is a significant amount of literature on creatine supplementation, however, there is limited data regarding the safety of creatine (Mihic et al., 2000; Juhn and Tarnopolsky, 1998; Poortmans et al., 1997; Poortmans and Francaux, 2000). Most of the studies examining the potential adverse effects of creatine have focused on gastrointestinal symptoms, muscle cramping, and renal function. There have been a few anecdotal reports of nausea, vomiting, and diarrhea that have been associated with creatine supplementation, however, no direct relationship has been established (Gordon et al., 1995; Kreider et al., 1998;Vandenberghe et al., 1997; Volek et al., 1999). In addition, there have been anecdotal reports of muscle cramping, strains and stiffness in individuals supplementing with CrM. It has been hypothesized that the increased water retention observed with creatine supplementation may increase skeletal muscle compartment pressure causing muscle cramping and stiffness; however, performance studies that have used pure creatine have failed to support this observation (Gordon et al., 1995; Grindstaff et al., 1997; Kreider et al., 1998; Vandenberghe et al., 1997). Finally, there have been two case reports of creatine supplementation inducing renal dysfunction in young men (Koshy et al., 1999; Pritchard and Clarkson, 1998). However, studies investigating the effects of creatine supplementation upon indices of renal function have not reported any detrimental side effects (Mihic et al., 2000; Poortmans et al., 1997; Poortmans et al., 2000; Robinson et al., 2000).

2.10 Potential Benefits of Creatine Supplementation in the Elderly

Muscle atrophy, a decline in muscle strength, and a reduction in high energy phosphates are common characteristics in the elderly and other disease conditions including congestive heart failure (Gordon et al., 1995), mitochondrial cytopathy (Arnold et al., 1985; Matthews et al., 1991; Tarnopolsky and Parise, 1999), and muscular dystrophy (Tarnopolsky and Parise, 1999). Therefore, strategies that may override these effects could have functional significance for these individuals. To date, oral creatine supplementation has been used to therapeutically replenish total creatine levels in muscle of patients with gyrate atrophy (Sipila et al., 1981), McArdle's disease (Vorgerd et al., 2000), neuromuscular disease (Tarnopolsky et al., 1997), muscular dystrophy (Walter et al., 2000), congestive heart failure (Andrews et al., 1998; Gordon et al., 1995), and rheumatoid arthritis (Willer et al., 2000).

There appears to be an enhanced ability to increase intramuscular TCr and PCr stores when endogenous stores are lower than normal (Harris et al., 1992). In general, the lower the initial intramuscular TCr stores, the greater the creatine uptake into muscle (Gordon et al., 1995; Harris et al., 1992; Casey et al., 1996). Advancing age is associated with reductions in intramuscular TCr and PCr concentrations (Campbell et al., 1999; Forsberg et al., 1991; Smith et al., 1998). Studies using muscle biopsies (Campbell et al., 1999) and ^{31}P-magnetic resonance spectroscopy (^{31}P-MRS) (Smith et al., 1998) have reported that healthy elderly men and women (58-75 years) have significantly lower PCr and TCr concentrations as compared to

young healthy men and women (19-30 years) Smith and colleagues (1998), using ^{31}P-MRS, found that that middle-aged individuals (58 ± 4.5) had significantly lower resting muscle PCr compared with younger individuals (31 ± 5.2). Similarly, Campbell and colleagues (1999) found that muscle TCr concentrations were lower in older men (51 to 69 years) than in young men (Harris et al., 1992). Moreover, the values for the elderly are comparable to those seen in neuromuscular patients (Tarnopolsky and Parise, 1999). Thus, it is possible, that these individuals may be at a disadvantage in activities requiring rapid energy turnover rates. Given the observed reductions in TCr and PCr in older adults (Campbell et al., 1999; Smith et al., 1998), it may be possible for creatine supplementation to optimize the availability of high-energy phosphates in those individuals whose intramuscular TCr levels are lower than normal. Furthermore, creatine supplementation may attenuate age related muscle atrophy and loss of strength and increase FFM in older adults.

2.11 Creatine Supplementation Studies in Older Adults

There have been a limited number of studies examining the potential efficacy of creatine supplementation in enhancing muscle function in older adults (Table 3). Three studies have examined the effects of acute creatine supplementation in older adults. Rawson and Clarkson (1999) examined the effects of 5 days of creatine supplementation (20 g/d) in 17 healthy older men (60 to 78 years). Body composition (bioelectrical impedance and anthropometry), elbow flexor isometric strength, and isokinetic knee extension performance were measured. Following creatine

supplementation, there was a 0.5 kg increase in TBM, a small improvement in isokinetic knee extension performance and no change in elbow flexor maximal isometric strength.

More recently, Jakobi and colleagues (2001) examined the effects of acute creatine supplementation in 12 older men (65 to 82 years). Subjects consumed either 20 g of CrM or placebo for 5 days. Measures of body composition (anthropometry), and maximal isometric voluntary force, muscle activation, contractile properties, and surface electromyography in the elbow flexors were completed. Following creatine supplementation, there was a 1 kg increase in TBM as compared to placebo (Jakobi et al., 2001). There was no effect of creatine supplementation on muscle strength and fatigue in the elbow flexor muscles.

Using a single-blind crossover protocol, Smith and colleagues (1998) examined the effects of creatine supplementation (0.3 g/kg body weight for 5 days) on PCr resynthesis rates and basal concentrations in young (31 ± 5.2 years) and middle-aged (58 ± 4.5 years) subjects using ^{31}P-MRS. Each subject performed two 2-minute bouts of single-leg knee extension exercise followed by a third bout until exhaustion separated by 3 minutes of recovery on 2 different days. Resting and recovery PCr was lower in the middle aged groups compared with the young group. Following creatine supplementation, resting and recovery PCr increased in the young and middle-aged groups by 15% and 30%, respectively. Therefore, after creatine supplementation, resting PCr was increased so that similar values were obtained in both age groups. Furthermore, time to exhaustion was significantly increased in the

creatine supplementation group as compared to placebo in both young and middle aged subjects (Smith et al., 1998).

There have been two studies that have examined the chronic effects of creatine supplementation in older adults (Bermon et al., 1998; Rawson et al., 1999). In a double blind manner, Rawson and colleagues (1999) randomly assigned 20 older men (60 to 82 years) to receive either creatine or placebo for 30 days. Subjects ingested either 20 g of creatine or placebo for 10 days followed by 4 g of creatine or placebo for 20 days. Measures of leg fatigue, elbow flexor strength, and body composition (hydrostatic weighing) were assessed before and after supplementation. There was a significant group by time interaction in leg fatigue following supplementation with the creatine group demonstrating an 8% increase in performance. There was no treatment effect found for measures of body composition (TBM, FFM, %BF) or muscle strength.

To date, there has only been one study looking the combined effects of creatine supplementation and resistance training (Bermon et al., 1998). In this study, 16 males and 16 females were randomly assigned to 4 groups (control-creatine, control-placebo, trained-creatine, trained-placebo). The creatine group consumed 20 g of creatine daily for the first 5 days, followed by 3g/d, while the others consumed placebo for 8 weeks. The training program consisted of 3 exercises (leg press, knee extension, and seated chest press) that were performed three times/week for seven weeks. The trained group had significantly greater improvements in muscle strength (leg press, chest press, leg extension) than the control group. There were no

significant interactions between supplementation and training or time in any exercise. Also, there were no significant interactive effects of either training or creatine supplementation on TBM and LBM, as determined by anthropometry.

Table 3. Summary of the studies examining creatine supplementation in the elderly.

Authors	Year	Sample Size	Age	Suppl Period	Training	Measures	Results
Rawson and Clarkson	1999	17 M	60-78	5 days (Cr or Pl)	None	Arm isometric strength (elbow flexors, 3 max) Leg Fatigue (3sets x 30 reps, knee ext) Body Composition (skinfolds, circumference, BIA)	No differences b/w groups No change 0.5 kg ↑ in Cr group
Rawson *et al.*	1999	20 M	60-82	30 days (Cr or Pl)	None	Arm isometric strength (elbow flexors, 3 max) Leg fatigue (5sets x 30 reps, knee ext) Body composition (hydrostatic weighing)	No differences b/w groups (sm ↑ in both groups) 8%↑ in Cr group No Change
Bermon *et al.*	1998	16 M 16 W	67-80	52 days (Cr or Pl)	8 weeks of RT (control or training)	Strength Training (leg press, knee ext, chest press – 3 sets, 80% 1RM) 1RM, 12RM, IIE Body Composition (skinfolds)	No effect of Cr No Change
Smith *et al.*	1998	Young (4m,1w) Midage (3m,1w)	31±5.2 58±4.5	5 days (Pl then Cr)	None (3 acute exercise bouts)	^{31}P-MRS measures of PCr Rate of PCr resynthesis Time to exhaustion	Pl – mid age<muscle PCr, resynthesis rate ↓ in mid aged Cr – young ↑PCr by 15% mid age ↑PCr by 30%

Note -- The outcome variables have not included direct muscle biopsy measurements of PCr/Cr/ATP nor muscle morphology.

2.12 Rationale for Study

There have been a limited number of studies examining the potential benefits of creatine supplementation on body composition (TBM, FFM, %BF) and physical performance in older adults (Bermon et el., 1998; Jakobi et al., 2001; Rawson and Clarkson, 1999; Rawson et al, 1999; Smith et al., 1998). Recently, we and others have reported that with aging there is a reduction in intramuscular TCr (Campbell et

al., 1999) and PCr concentration (Smith et al., 1998). It is possible that this may be one of many factors that contributes to muscle atrophy and weakness that accompanies the aging process. Preliminary studies have reported that creatine is well tolerated in individuals over the age of 65 years and that there is a slight increase in strength (Rawson and Clarkson, 1999; Rawson et al., 1999). Unfortunately, small sample sizes and poor outcome variables have limited the outcomes of these studies. In addition, most of the studies were very short in duration and only one other study has examined the combined effects of creatine supplementation and resistance training in an older population (Bermon et al., 1998). Thus, the beneficial effects of creatine on body composition and muscle function remain to be demonstrated in an elderly population.

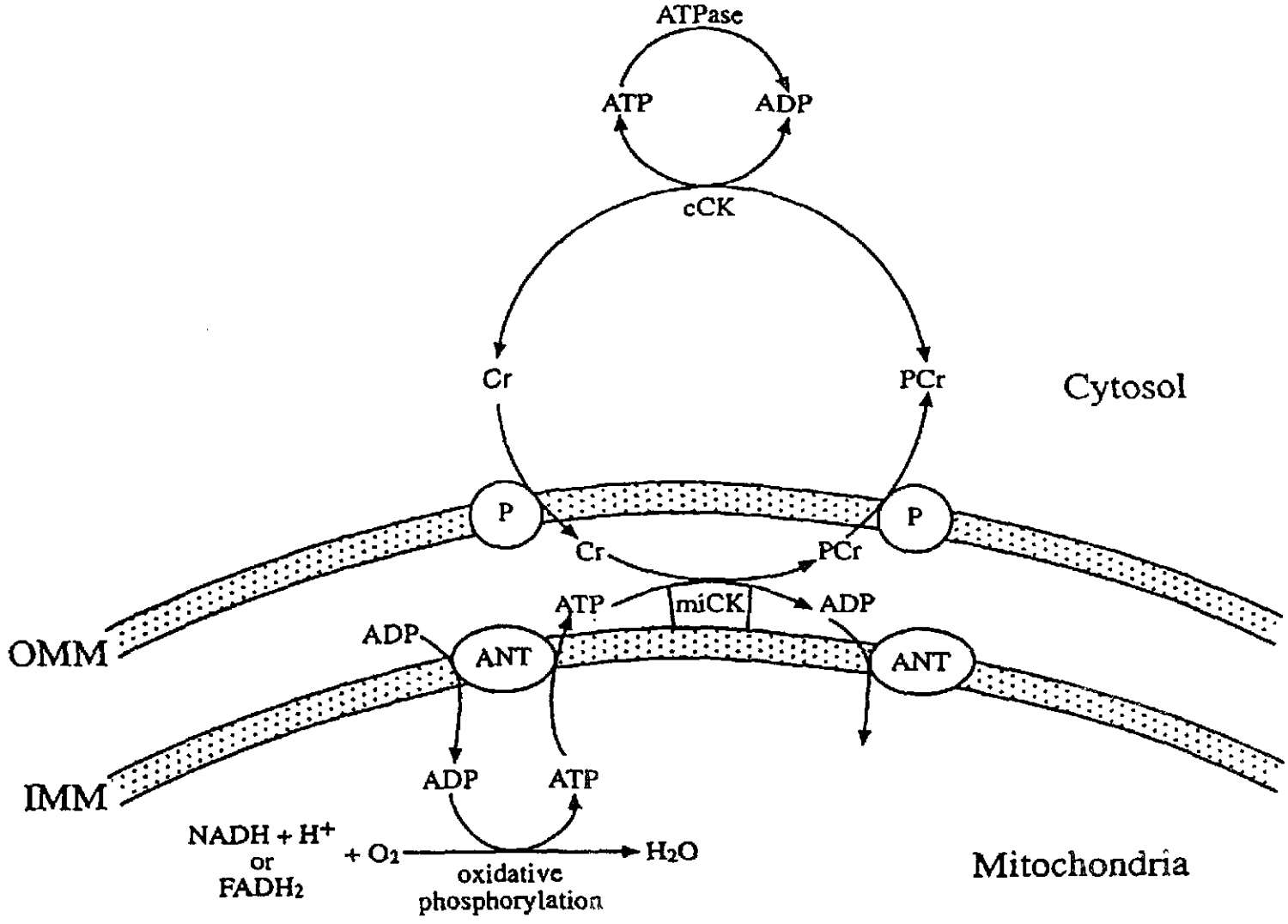
2.13 Purpose of Study

The purpose of the present investigation was to determine the independent and interactive effects of creatine supplementation and resistance training on physical performance, body composition, and intramuscular total creatine concentration in older men and women. Furthermore, we chose to examine the effects of creatine supplementation and resistance training on skeletal muscle morphology, as the effects of creatine supplementation during exercise training have not been investigated in older adults. We hypothesized that resistance training would: 1) increase muscle strength and FFM; and 2) increase functional capacity in elderly men and women. Furthermore, we hypothesized that the creatine group would 1) experience greater

improvements in strength and FFM; and 2) increase skeletal muscle TCr and PCr content.

improvements in strength and FFM; and 2) increase skeletal muscle TCr and PCr content.

Fig 2. Spatial Characteristic of PCr Energy System



Taken from Juhn and Tarnopolsky, 1998.

Introduction

Physical disability and functional dependency related to aging are becoming more prevalent in our society leading to an increased consumption of health care resources and increased admission to nursing homes (Schneider and Guralnik, 1990). Recently, Guralnik and colleagues (1995) reported that lower extremity physical performance is predictive of the subsequent development of disability in healthy older individuals. Furthermore, muscle strength and power are, in part, primary determinants of functional dependence and are correlated to walking speed, stair climbing, and the ability to rise from a chair (Bassey et al., 1992). Ultimately, a progressive decline in functional capacity will result in a lack of physical activity, impaired mobility, increased risk of falls, a loss of independence, and disability. Therefore, the maintenance of muscle mass and strength may have important health implications in an older population.

Reductions in total muscle mass, fat-free mass (Novak, 1972), and muscle strength (Larsson et al., 1979) have been well documented in healthy older adults. The etiology underlying these age-related changes in body composition and strength are complex and multifactorial. A reduction in type II fiber area (Grimby et al., 1982; Larsson et al., 1979) and fiber number (Lexell et al., 1988), a loss of motor units (Doherty et al., 1993), a decline in anabolic hormone levels (Birkenhager-Gillesse, 1994; Morley et al., 1997; Zadik et al., 1995), and disuse are inter-related components of the aging process that ultimately contribute to sarcopenia. Therefore,

understanding the etiology of the aging process and the potential for reversibility assumes critical importance.

Resistance training has been consistently shown to attenuate or partially reverse age-associated decrements in muscle strength and mass in older males (Frontera et al., 1988) and females (Charette et al., 1991). Furthermore, in most, but not all studies, resistance exercise has been shown to increase fat-free mass in older people (Ades et al., 1996; Taaffe et al., 1999; Treuth et al., 1994). Finally, an increase in functional capacity and independence and a decrease in frailty has also been documented following resistance training, even in very old (>90 years) men and women (Fiatarone et al., 1990).

Creatine is a guanidino compound found in exogenous food sources such as meat and fish, and is produced endogenously by the liver, kidney, and pancreas. Creatine monohydrate supplementation during resistance training has been shown to increase strength (Vandenberghe et al., 1997), total lifting volume (Kreider et al., 1998; Volek et al., 1999), muscle fiber area (Volek et al., 1999), total body mass (Kreider et al., 1998; Vandenberghe et al., 1997; Volek et al., 1999), fat free mass (Kreider et al., 1998; Vandenberghe et al., 1997; Volek et al., 1999) and intramuscular total creatine (Volek et al., 1999) and phosphocreatine (Vandenberghe et al., 1997) stores as compared to placebo in young men and women. The beneficial effects of creatine on performance are inversely proportional to the total creatine concentration in skeletal muscle (Harris et al., 1992). Recently, we and others have reported that the intra-muscular total creatine concentration is ~25% lower in older (Campbell et al., 1999)

and middle-aged adults (Smith et al., 1998) as compared to young individuals (Harris et al., 1992). Reduced muscle total creatine concentration may, in part, be responsible for the observed reductions in muscle strength. Thus, older individuals may show a propensity for an improvement in performance following creatine supplementation.

There have been a limited number of studies examining the potential benefits of creatine supplementation on body composition and physical performance in older adults (Bermon et al., 1998; Jakobi et al., 2001; Rawson and Clarkson, 1999; Rawson et al., 1999; Smith et al., 1998). Acute creatine supplementation has been found to increase total body mass and isokinetic performance in elderly men (Rawson and Clarkson, 1999). Furthermore, Smith and colleagues (1998) observed an increase in muscle phosphocreatine and an improved time to exhaustion during knee extension after 5 d of creatine supplementation in healthy middle-aged subjects vs. younger subjects. In addition, one study has examined the combined effects of creatine supplementation and resistance training (Bermon et al., 1998). The improvements in muscle strength observed with training were similar for both the creatine and placebo group. Thus, the beneficial effects of creatine on body composition and muscle function are inadequately evaluated in older adults.

The purpose of the present investigation was to determine the effects of creatine supplementation and resistance training on physical performance, body composition, and intramuscular total creatine concentration in older men and women. Furthermore, we chose to examine the effects of creatine supplementation and

resistance training on skeletal muscle morphology, as the effects of creatine supplementation during exercise training have not been investigated in an older population. We hypothesized that resistance training would: 1) increase muscle strength and fat free mass; and 2) increase functional capacity in older men and women. Furthermore, we hypothesized that the creatine group would: 1) experience greater improvements in strength and fat free mass; and 2) increase skeletal muscle total creatine and phosphocreatine.

Methodology

Subjects.

Fifteen men (67.8 ± 4.0 yr) and 15 women (69.3 ± 6.3 yr) volunteered to participate in a 14-wk resistance training program. Each subject underwent a thorough screening procedure which included a telephone interview, a medical evaluation, consent from a family physician, a resting electrocardiogram, and a submaximal graded exercise test on a bicycle ergometer. Exclusion criteria included: evidence of coronary heart disease; congestive heart disease; uncontrolled hypertension; chronic obstructive pulmonary disease; diabetes mellitus; renal failure; major orthopedic disability; and smoking. All the women were postmenopausal and were not currently taking hormone replacement therapy. Although none of the subjects had previously participated in a structured resistance training program, all were moderately active and engaged in periodic low-intensity physical activity consisting of tennis, golf, and walking. After receiving a description of the study

procedures and advisement of the risks and benefits of participation, all subjects gave their written informed consent. The study was approved by the McMaster University Medical Ethics Committee and conferred to the principles of the Declaration of Helsinki.

Of the original 30 volunteers, a total of 15 males and 13 females completed all aspects of the study. Two females, one from each group, dropped out of the study for personal reasons.

Nutritional Supplementation.

On the first day of the resistance training program, subjects were randomly assigned in a double blind manner to either a creatine monohydrate (CrM) (Neotine, Avicena, Cambridge, MA) or a placebo (PL) group. The CrM group consisted of 8 men and 6 women, while the PL group consisted of 7 men and 7 women (Table1). Subjects in the CrM group consumed 5g CrM + 2g of dextrose per day, while the PL group consumed 7g dextrose per day for 14 weeks. The flavour and appearance of the supplements were indistinguishable by the subjects and the investigators. Subjects were instructed to consume their supplement dissolved in juice. Subjects returned their empty packets on a weekly basis to ensure compliance. A 3-day dietary recall was completed (2 weekdays, 1 weekend day) prior to and after the training period. The diets were analyzed using a commercially available software program (Nutritionist V, First Data Bank, San Bruno, CA), and the subjects were asked to maintain similar dietary patterns during the study.

Strength Training.

Training was conducted three times weekly on nonconsecutive days (Monday, Wednesday, and Friday) for 14 weeks. Each training session was preceded by a 5-minute warm-up, followed by static stretching of all major muscle groups. In addition, each session was followed by a cool down period consisting of stretching of the muscle groups involved in the resistance exercises. Exercises were performed in a circuit set system, with a 2-minute rest between sets. Twelve exercises were used to train the major muscle groups of the upper and lower body: seated chest press, latissimus pull-down, leg press, military press, calf raise, arm extension, are flexion, back extension, abdominal crunch, upright row, knee extension, and knee flexion. Subjects performed 10 repetitions of each arm exercise and 12 repetitions of the remaining exercises. Training progressed from one set of each exercise at 50% of the initial 1 repetition maximum (1 RM) to three sets at 80% of 1 RM over the training period. Training logs were kept to record the volume and intensity of each session and each session was individually monitored by a research coordinator. The 1 RM was re-evaluated every 2 weeks, and the training loads were adjusted accordingly. All subjects were supervised and instructed on proper techniques throughout the study. All training was performed on universal strength training equipment (Universal Gym Equipment, Inc., Cedar Rapids, Iowa).

Testing.

All testing procedures were conducted before and after 14 weeks of resistance training. The post testing was conducted at 48 h following the last exercise bout.

i. Dynamic strength testing

Before initial strength testing, two low-intensity resistance training sessions were completed to habituate the subjects to the training equipment, proper exercise techniques, and training protocol. In the second session, 1 RM was used to assess strength in four different exercises (upright chest press, leg press, arm flexion, and knee extension). 1 RM was defined as the highest resistance at which one repetition could be successfully completed with acceptable form.

Before the 1 RM testing session, each subject cycled for 5 minutes on a stationary cycle and then stretched the major muscle groups to be tested. Each subject was required to do three warm-up lifts at a very low resistance. Thereafter, a resistance was chosen that was thought to be slightly below the 1 RM value to minimize fatigue resulting from repetition. The subject performed one repetition of the exercise. After 2 minutes of rest, another attempt was made against a higher resistance until a final value was obtained. Testing took place on two different days and the heaviest weight lifted was recorded as the pre-training value. The preliminary 1 RM values were used to calculate the initial training load of 50% of 1 RM. 1 RM testing was conducted again at the end of the training program. In addition, at the end

of the training program, each subject performed as many repetitions as possible with the pre-training 1 RM to provide a measure of endurance. The same investigator measured 1 RM strength before, during, and after training. All testing procedures were standardized with respect to specific seat adjustments and body positions.

ii. Isometric Strength

Handgrip muscle strength, ankle dorsiflexion strength, and knee extensor strength were all measured using custom made isometric devices as previously described (Tarnopolsky et al., 1997; Tarnopolsky and Martin, 1999). For all three measures, subjects performed three maximal voluntary contractions, each being 5-seconds in duration. A 1-minute rest was given between each repetition. The best performance in the three trials was recorded as the maximal value.

iii. Functional testing

Three functional ability tests (30-second chair stand, timed walk and timed stair climb) were performed in subjects before and after training. The 30-second chair stand test required subjects to rise up and sit down as quickly as possible on a firm, armless chair placed against a wall. The subjects were instructed to fold their arms across their chest before beginning the test. The total number of times that subjects could fully stand in 30 seconds was recorded (Rikli and Jones, 1999). The timed stair climb required subjects to walk as fast as possible up 14 stairs without the use of railings. The timed walk required subjects to walk a distance of 30 meters as

fast as possible without the use of external aids. All times were recorded using a digital stopwatch.

iv. Body composition assessment

Body mass and height were measured to the nearest 0.1 kg and 0.5 cm, respectively, using a calibrated electronic scale (Healthometer Pro Series Electronic Scale, Bridgeview, IL). Subjects were weighed at approximately the same time of day before and after training. A total body scan was performed using dual-energy X-ray absorptiometry (Hologic QDR® 4500A; Waltham, MA) to determine body fat percentage (%BF), fat mass (FM), and fat/bone free mass (FFM). A calibration standard was scanned daily, and measurement accuracy was ensured by scanning a spine phantom of known proportions. All scans were analyzed using the Hologic software program (v., 8.26a) for body composition analyses.

v. Muscle, Blood, and Urine Collection

Muscle biopsies (~100 mg) were obtained from the *vastus lateralis* muscle of the dominant leg under local anesthesia (1% lidocaine) using a modified Bergström needle biopsy technique (Bergström, 1962), with suction modification. All visible fat and connective tissue was dissected free from the biopsy sample. One section of muscle was mounted in embedding medium (optimum cutting temperature compound (OCT), Tissue-Tek, Torrance, CA) on cork with the aid of a microscope for histochemical analysis. The sample was frozen in liquid isopentane (2-methlybutane;

Fisher Scientific, Fair Lawn, NJ), cooled in liquid nitrogen, and subsequently stored at -80°C for further analysis. A second sample (~10-30 mg) was frozen in liquid nitrogen 60 seconds after obtaining the specimen (Söderlund and Hultman, 1986) and stored at -80°C for subsequent analysis of creatine (Cr), phosphocreatine (PCr), and adenosine triphosphate (ATP) concentrations (see below).

Blood was drawn from an antecubital vein into 10-ml non-treated tubes (serum), and 5-ml ethylenediaminetetraacetic acid (EDTA)-treated tubes (plasma). The serum sample was stored at room temperature to allow the blood sample to clot. All tubes were centrifuged at 1200 rpm for approximately 5 min. Serum and plasma were separated from blood cells and stored at -70°C for subsequent analysis of total testosterone (TT), insulin-like growth factor-1 (IGF-1), dehydroepiandrosterone sulfate (DHEAS), osteocalcin (OC), creatine kinase activity (CK), γ-glutayltransferase activity (GGT) and creatinine (Crn) (see below). Thereafter, a urine sample was collected for subsequent analysis of Crn and creatine (Cr).

Tissue Analysis.

i. Histochemistry

Muscle samples were cut into transverse sections (8 μm) in series using a cryostat (Microtome HM500OM, Microm International, Walldorf, Germany) with sample and cabinet temperatures at -20°C and mounted on glass slides. Prior to histochemical analysis, each muscle sample was stained with hematoxylin and eosin and examined by light microscopy to ensure that all fibers were in cross-section. The

cross sections were stained for myofibrillar adenosinetriphosphatase (mATPase) activity at pH 9.4 following preincubation at pH 4.48 to differentiate type I, type IIa and type IIx fibers (Brooke and Kaiser, 1970). In this preparation, the type I fibers stain darkly, type IIa fibers stain lightly, and type IIx fibers stain intermediately (see figure 1). The stained slides were photographed (Spot camera, Diagnostics Instruments, Inc., Sterling Heights, MI) under a light microscope (Olympus BX60, Melville, NY) for examination of fiber type (10x magnification) and fiber cross-sectional area (40x magnification). Samples were analyzed using a commercially available computer image analysis software (Image Pro® Plus, Version 4.0 for windows, Media Cybernetics, Silver Spring, MD) to determine mean single fiber cross-sectional area. An average of, 425±102 (range 252-683) fibers were counted per biopsy for determination of muscle fiber type and mean fiber area. Only those fibers without artifact, with distinct cell borders, and no tendency toward longitudinal cuts were included in the analysis of mean fiber area.

ii. Metabolites

Muscle samples frozen in liquid nitrogen were lyophylized, powdered, and dissected free of any connective tissue. The powdered tissue (5-10 mg dm) was weighed into a 1.5 ml polyethylene tube and extracted in 0.5 M perchloric acid containing 1 mM EDTA at a ratio of 800 μL to every 10 mg powder for 5 minutes on ice while vortexing. The samples were then centrifuged for 5 min at 7000 rpm and neutralized using 2 M $KHCO_3$. Extracts were then centrifuged for 15 min at 7000

rpm, and the supernatant was stored in a 1.5 mL polyethylene tube at -50°C. Subsequently, the extracts were analyzed for ATP, PCr, and Cr using an enzymatic method that has recently been described in detail by our group (Tarnopolsky and Parise, 1999).

Briefly, ATP and PCr were assayed in the presence of 50 mM Tris buffer, pH 7.4; 1 mM magnesium chloride, 0.5 mM dithiothreitol, 100 μM glucose, 50 μM NADP, 350 U/mL glucose-6-phosphate dehydrogenase. The assay was carried out in 1-mL cuvettes using 10 μL of sample to 1 mL of reagent. The reaction solution was vortexed and read using a fluorometer (Hitachi F-2500 Fluorescence SpectroPhotometer, Chromabec HPLC Inc., St. Laurent, QC) at a wavelength of 340 nm. For ATP analysis, 25 μL of hexokinase solution (25 mL of hexokinase (280 U/mL) added to 1 mL of reagent) was added to the tube, vortexed, incubated in the dark for 30 min, and again read in the fluorometer. For PCr analysis, 20 μL of CK/ADP solution (2 mg of CK (25 U/mg) and 2 ng ADP added to 1 mL of reagent) was added to the tube, vortexed, incubated in the dark for 60 min, and again read in the fluorometer.

Creatine was assayed in the presence of 50 mM imidazole buffer, pH 7.4; 5 mM magnesium chloride, 30 mM potassium chloride, 25 μM phosphoenolpyruvate, 200 μM ATP, 45 μM NADH, 1250 U/mL lactate dehydrogenase, and 2000 U/mL pyruvate kinase. 5 mg of CK (25 U/mg) was added to 1 mL of the above buffer and stabalized using 10% bovine serum albumin. The assay was carried out in 13 x 75 glass screw top tubes using 10 μL of sample in 1 mL of reagent. The reaction

solution was vortexed, incubated in the dark for 15 min, and read in the fluorometer at a wavelength of 340 nm. 25 μL of creatine kinase buffer solution was then added to the sample, vortexed, incubated in the dark for 30 min, and read on the fluorometer.

Intra-assay CV for ATP, PCr, and Cr were 7.3%, 8.5%, and 8.4% respectively. Any values that were >2 SD from the mean were re-run on a separate piece of muscle. Intramuscular TCr concentration was calculated as the sum of Cr and PCr concentrations.

Blood and Urine Analysis.

TT, IGF-1, and CK were analyzed in plasma samples, while DHEAS, OC, GGT, and creatinine were analyzed in serum samples. TT (Coat-A-Count®, Diagnostics Products Corporation, Los Angeles, CA), DHEAS (Coat-A-Count®, Diagnostics Products Corporation, Los Angeles, CA), and OC (Procedure no. BT-440, Biomedical Technologies Inc., Stoughton, MA) were analyzed by radioimmunoassay. The samples were counted for 1-min in a γ counter (Autogamma® 5000 Series Gamma Counter, Canberra Packard Canada, Ltd., Mississauga, ON) and the counts per minute were fitted to a standard curve to determine the final concentrations of each hormone. Intra-assay coefficient of variation (CV) was 3.4% for TT, 4.1% for DHEAS, and 3.9% for OC, respectively. IGF-1 was analyzed by a two-site immunoenzymometric (IEMA) assay (Procedure no. AC-27F1, ALPCO Diagnostics, Windham, NH). The intra-assay CV was 1.9%.

CK activity was determined using a commercially available enzyme assay kit (Procedure no. 661, Sigma Diagnostics, St. Louis, MO) The intra-assay CV was 5.0%. Serum Crn was determined using a commercially available enzymatic kit (Procedure No. 555, Sigma Diagnostics, St. Louis, MO). Intra-assay CV was 2.5% for serum Crn. Serum GGT was measured using an autoanalyzer (Kodak, Ektachem, Rochester, NY) by the clinical chemistry department. All samples were run in duplicate.

Statistical Analysis.

Values are reported as mean ± SD. All statistics were performed using a commercially available software program (version 5.0, Statistica, Statsoft, Tulsa, OK). All variables were analyzed using a three-way, repeated measures analysis of variance: a 2 (condition: Cr vs. Pl) x 2 (gender: male vs. female) x 2 (time: pre- vs. post- training) design, with repeated measures on the last factor. A p level of < 0.05 was used to determine significance, and significant differences were further analyzed using Tukey's post hoc test.

Results

Subject characteristics and body composition.

At baseline, the treatment groups were comparable in age, height, weight, %BF and FFM. As expected, men were significantly taller, had greater FFM, TBM

and lower %BF, and had higher daily energy (kcal/day) and protein (g PRO/kg/d) intakes as compared to women ($p<0.05$). No significant differences were observed between groups in mean estimated total energy intake. Furthermore, the proportion of protein, fat, and carbohydrate was not different between groups. Neither the energy intake nor the protein, fat, and carbohydrate composition of the diet was changed during the training period. Physical characteristics and dietary analysis are presented in Table 1.

Following resistance exercise training, there was a significantly greater increase in TBM (1.2 ± 1.7 kg) and FFM (1.7 ± 1.2 kg) for CrM supplementation, as compared to PL (TBM: -0.2 ± 1.3 kg; FFM: 0.4 ± 0.5 kg) (Table 2, Figure 2; group x time interaction, $p<0.05$). There was no significant change in %BF or FM over the training period.

Side Effects.

Subjects tolerated the supplementation protocol well with only 2 reports of gastrointestinal distress (one in each treatment group). In addition, there was no reports of muscular cramping or any other subjective symptoms during the entire length of the study.

Muscle high-energy phosphates.

At baseline, the concentrations of muscle free Cr, PCr, and TCr were not significantly different between groups, nor were there any gender differences. CrM

supplementation increased muscle TCr by 27.0% (men: pre: 116.8 ± 14.5 mmol•kg^{-1} vs. post: 159.3 ± 23.9 mmol•kg^{-1}; women: pre: 129.7 ± 25.4 mmol•kg^{-1} vs. post: 151.7 ± 18.7 mmol•kg^{-1}) (group x time interaction, $p<0.01$). In addition, the increase in TCr was greater for men as compared to women (group x gender x time interaction, $p<0.05$). Finally, CrM supplementation had no effect on free Cr, PCr or ATP concentrations (Table 3).

Isometric Strength.

At baseline, there were no significant between-group differences for any of the three isometric strength measures. The men were significantly stronger than the women in all three exercises ($p<0.001$). There was a significant increase in knee extensor strength for all groups, however, the increase for the creatine group was greater (46.2 ± 22.5%) as compared to the placebo group (22.5 ± 14.4%) for both genders (Figure 3; group x time interaction, $p<0.05$). There was a significant increase in dorsiflexion strength for all groups, however, the increase in the creatine group was greater (17.8 ± 11.6%) than placebo, only for the men ($p<0.05$). There was no effect of training or supplementation on handgrip strength. Isometric strength measures are represented in table 4.

Dynamic Strength.

At baseline, the men in the CrM group had a significantly higher 1 RM in arm flexion as compared to the men in the PL group ($p<0.05$). There were no other

between group differences in baseline 1 RM for the remaining strength measures. The men had greater maximum voluntary muscle strength (1 RM) than the women on all four exercises tested ($p<0.001$; Table 4). Following training, 1 RM strength increased significantly in all four exercises ($p<0.001$; Table 4). There was no additional effect of CrM supplementation on the increase in strength for any of the 4 exercises. The male subjects improved their 1 RM (absolute) significantly more than the females in both the arm flexion and seated chest press (gender x time, $p<0.05$). In addition, the absolute endurance was significantly increased after training, such that subjects were able to lift their pre-training 1 RM an average of 31, 13, 13, and 12 times, in the leg press, knee extension, arm flexion, and chest press, respectively ($p<0.001$).

Muscle histology.

On average, 425 ± 103 fibers per subject were counted for pre-training analysis, and 439 ± 133 fibers were counted for post-training analysis. Fiber type distribution was not significantly different after training for any group. Type I, type IIa and type IIx mean fiber areas were significantly greater in men than women ($p<0.05$). Following the training program (collapsed across gender and condition) there was a significant increase in the mean fiber area for type I ($p<0.05$) and type IIx ($p<0.001$) fibers but not type IIa fibers. The mean fiber area increased more in the type IIx fibers than type I fibers with training; consequently, there was a significant increase in the type IIx:type I area ratio ($p<0.05$). In addition, the men had a greater

percentage area of type IIx fibers ($p<0.05$) and smaller percentage area of type I fibers ($p<0.05$) than the women. Muscle fiber areas, percentage area, and fiber type distributions are shown Table 5. A representative histochemical stain is shown in Figure 1.

Functional Measures.

There was a significant effect of training on performance in each of the functional tests. The number of chair stands that could be performed in 30 seconds after training increased by 3.4, representing a 23.0% increase in performance ($p<0.001$). Training also improved the 30 m walk by 1.7 seconds (11.1% decrease in time) ($p<0.001$) and the time to climb 14 stairs improved by 1.2 seconds (23.5% decrease in time) ($p<0.001$). In addition, the males were significantly faster than the females in the timed 30 m walk ($p<0.05$).

Blood and Urine Analyses.

Plasma Crn concentration was increased for the CrM group following training (men: 13% increase; women: 22% increase) ($p<0.05$). Plasma CK activity was also significantly higher in the CrM group after training as compared to the PL group ($p<0.05$). The urine creatine:creatinine ratio was significantly increased in the creatine group ($p<0.05$). There were no effects of treatment or training upon TT, IGF-1, DHEAS, OC, GGT, or urine Crn concentrations. Finally, the men had significantly higher TT ($p<0.001$) and DHEAS ($p<0.05$) concentrations as compared to the women (Table 6).

Table 1. Subject characteristics and dietary analysis before training.

	Creatine		Placebo	
	Men	Women	Men	Women
Age, yr	68.3 ± 4.8	70.5 ± 7.1	67.3 ± 3.2	68.3 ± 5.9
Height, cm	172.0 ± 6.3*	159.3 ± 6.9	168.1 ± 4.9*	160.4 ± 7.7
Weight, kg	84.1 ± 14.0*	65.4 ± 16.2	76.6 ± 9.8*	66.2 ± 13.7
Energy Intake				
Kcal/d	2249 ± 488*	1821 ± 457	2603 ± 587*	1788 ± 507
% PRO	16 ± 2	16 ± 3	16 ± 3	16 ± 4
% CHO	54 ± 6	50 ± 7	49 ± 12	46 ± 12
% FAT	29 ± 5	33 ± 5	30 ± 6	30 ± 5
PRO (g/d)	91.1 ± 18.7*	71.1 ± 19.8	104.3 ± 27.4*	73.3 ± 25.2

Values are means ± SD. * Significantly different from females ($p<0.05$).

Table 2. Body composition before and after training.

	Creatine				Placebo			
	Men		m		Men		Women	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
TBM, kg*	84.1 ± 14.0	85.5 ± 13.5†	65.4 ± 16.2	66.5 ± 16.8†	76.6 ± 9.8	76.2 ± 9.71	66.2 ± 14.0	66.2 ± 13.7
FFM, kg*	56.0 ± 7.1	57.4 ± 7.4†	33.7 ± 3.7	35.7 ± 4.1†	52.0 ± 5.3	52.0 ± 5.8	37.2 ± 1.8	37.8 ± 2.0
FM, kg	22.0 ± 5.4	22.3 ± 5.8	21.4 ± 9.7	17.3 ± 12.1	12.2 ± 2.9	12.1 ± 3.0	24.2 ± 11.2	23.9 ± 11.8
BF, %*	27.0 ± 3.9	26.8 ± 4.7	36.2 ± 11.8	34.2 ± 9.9	18.3 ± 2.1	18.1 ± 2.0	36.4 ± 11.2	35.5 ± 12.6

Values are mean ± SD. * Significantly different from females ($p<0.05$). † Indicates a significant group x time interaction with the creatine group showing an increase after training ($p<0.05$). Males, creatine (n=5); Females, creatine (n=5); Males, placebo (n=2); Females, placebo (n=4) for FFM, FM, and % BF. Males, creatine (n=8); Females, creatine (n=6); Males, placebo (n=7); Females, placebo (n=7) for TBM. TBM, total body mass; FFM, fat/bone-free mass; BF, body fat.

Table 3. Muscle metabolites before and after training.

	Creatine				Placebo			
	Men		Women		Men		Women	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
PCr	67.4 ± 19.7	88.0 ± 20.5	83.1 ± 15.2	91.1 ± 30.3	89.2 ± 25.6	70.7 ± 19.3	74.8 ± 13.8	85.2 ± 12.8
Cr	49.4 ± 16.0	71.3 ± 10.9	46.6 ± 13.8	60.6 ± 23.3	51.6 ± 22.9	54.7 ± 21.3	63.6 ± 15.9	62.4 ± 25.4
TCr	116.8 ± 14.5	159.3 ± 23.9 *	129.7 ± 25.4	151.7 ± 18.7*	140.8 ± 20.6	125.5 ± 25.4	138.5 ± 14.0	147.5 ± 20.3
ATP	18.1 ± 1.9	19.9 ± 6.1	17.0 ± 3.4	19.2 ± 3.9	20.3 ± 2.7	18.1 ± 3.9	18.9 ± 2.9	20.9 ± 2.6

Values are mean ± SD. * Indicates a significant group x time interaction with the creatine group showing an increase after training ($p<0.01$). Males, creatine (n=7); Females, creatine (n=6); Males, placebo (n=7); Females, placebo (n=6). All values are in $mmol \bullet kg^{-1}$ dm. PCr, phosphocreatine; Cr, free creatine; TCr, total creatine; ATP, adenosine triphosphate.

Table 4. Isometric and 1 RM measurements before and after training.

	Creatine				Placebo			
	Men[a]		Women		Men[a]		Women	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Isometric strength								
Grip (kg)	438 ± 63	469 ± 98	259 ± 67	259 ± 76	397 ± 56	406 ± 47	265 ± 31	267 ± 29
Dorsiflexion (Nm)	54 ± 14	62 ± 15 [f]	37 ± 4	40 ± 6 [c]	52 ± 8	52 ± 10 [c]	34 ± 9	39 ± 10 [c]
Knee extension (Nm)	153 ± 28	217 ± 36 [e]	94 ± 38	126 ± 30 [e]	156 ± 32	180 ± 29 [c]	89 ± 17	113 ± 25 [c]
1 RM strength (lbs)								
Seated chest press	116 ± 26	146 ± 33 [d]	48 ± 11	63 ± 21 [c]	97 ± 20	119 ± 15 [c]	46 ± 9	59 ± 11 [c]
Arm Flexion	81 ± 22[b]	112 ± 18 [d]	25 ± 7	40 ± 11 [c]	60 ± 16	85 ± 16 [c]	26 ± 8	40 ± 6 [c]
Leg press	194 ± 47	244 ± 55 [c]	111 ± 28	153 ± 54 [c]	166 ± 39	231 ± 33 [c]	105 ± 26	152 ± 30 [c]
Knee extension	119 ± 18	162 ± 24 [c]	71 ± 10	113 ± 22 [c]	107 ± 31	151 ± 32 [c]	73 ± 16	115 ± 30 [c]

Values are mean ± SD. [a] Significantly different from females ($p<0.001$). [b] Significantly different from placebo ($p<0.05$). [c] Significantly different from pre ($p<0.001$). [d] Indicates a gender x time interaction, with the males showing a larger increase after training ($p<0.05$). [e] Indicates a significant group x time interaction, with the creatine group showing a larger increase following training ($p<0.05$). [f] Indicates a group x gender x time interaction with the men in the creatine group showing a larger increase after training ($p<0.05$).

Table 5. Muscle fiber characteristics before and after training.

	Creatine				Placebo			
	Men		Women		Men		Women	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Mean Fiber Area (μm^2)								
Type I*	4856 ± 1331	5477 ± 1677†	3914 ± 857	4106 ± 1383†	4690 ± 1056	5827 ± 1388†	4326 ± 973	4558 ± 1459†
Type IIa*	5055 ± 1018	6105 ± 2230	3230 ± 1029	3037 ± 1030	4226 ± 615	5268 ± 1742	3138 ± 639	3237 ± 817
Type IIx*	3900 ± 1240	4998 ± 1796†	1808 ± 555	2542 ± 1204†	2899 ± 418	4076 ± 1611†	2250 ± 698	2633 ± 814†
% Area								
Type I*	40.5 ± 14.8	39.0 ± 16.3	58.3 ± 14.8	55.2 ± 12.4	41.6 ± 7.0	46.5 ± 12.7	53.8 ± 19.1	56.2 ± 17.5
Type IIa	39.0 ± 12.9	34.8 ± 4.4	30.5 ± 11.3	36.8 ± 12.2	40.5 ± 7.9	30.2 ± 4.8	30.6 ± 14.5	27.4 ± 9.7
Type IIx*	20.5 ± 18.8	26.2 ± 16.7	11.3 ± 10.0	9.4 ± 6.5	17.8 ± 11.2	23.2 ± 12.2	15.7 ± 11.3	16.4 ± 12.4
Fiber Distribution (%)								
Type I	40.6 ± 11.8	39.1 ± 13.7	51.5 ± 19.8	48.0 ± 11.2	37.1 ± 8.3	41.4 ± 7.9	45.5 ± 19.3	48.2 ± 17.2
Type IIa	37.3 ± 13.1	32.5 ± 2.9	30.0 ± 6.8	40.8 ± 13.6	39.5 ± 10.0	30.4 ± 7.5	32.4 ± 15.0	29.7 ± 9.7
Type IIx	22.0 ± 15.5	28.4 ± 14.7	18.5 ± 14.0	11.1 ± 7.9	23.4 ± 13.4	28.1 ± 11.7	22.2 ± 13.7	22.1 ± 14.2

Values are mean ± SD. * Significantly different from females ($p<0.05$); † Significantly different from pre ($p<0.05$).

Table 6. Blood analysis before and after training.

	Creatine				Placebo			
	Men		Women		Men		Women	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Blood analysis								
TT (nmol/L)*	15.4 ± 5.4	16.6 ± 4.9	0.7 ± 0.4	0.6 ± 0.4	19.3± 12.6	22.6 ± 6.3	0.3 ± 0.2	0.4 ± 0.4
DHEAS (μmol/L)*	3.7 ± 2.0	3.0 ± 1.8	2.3 ± 1.3	1.8 ± 1.3	2.8 ± 1.5	2.8 ± 1.6	1.7 ± 1.1	1.7 ± 1.0
IGF-1 (nmol/L)	10.5 ± 3.0	10.9 ± 3.3	10.2 ± 3.1	8.3 ± 4.0	9.0 ± 4.0	8.0 ± 1.3	7.3 ± 2.7	7.1 ± 1.3
OC (ng/mL)	16.0 ± 4.5	16.1 ± 2.7	17.1 ± 5.1	18.0 ± 5.0	14.1 ± 2.1	14.1 ± 1.8	16.3 ± 3.6	16.6 ± 3.6
CK activity (U/L)	53.3 ± 31.5	107.4 ± 76.4†	83.3 ± 85.0	112.3 ± 98.2†	83.7 ± 50.0	81.9 ± 43.8	67.6 ± 40.9	47.0 ± 22.1
Crn (μmol/L)	111.4 ± 24.4	126.2 ± 33.4†	95.4 ± 16.6	116.3 ± 16.3†	107.9 ± 30.3	95.7 ± 21.3	100.5 ± 19.4	89.3 ± 29.4
GGT (U/L)	31.4 ± 23.6	28.4 ± 17.7	17.7 ± 2.4	17.8 ± 3.5	24.7 ± 8.5	23.3 ± 6.9	28.0 ± 16.1	28.1 ± 15.4
Urine Analysis								
Cr (mg/mL)	0.8 ± 0.6	2.2 ± 2.1†	0.6 ± 0.4	3.9 ± 4.2†	0.4 ± 0.2	0.3 ± 0.2	0.4 ± 0.3	0.4 ± 0.4
Crn (mg/mL)	0.9 ± 0.4	1.0 ± 0.4	0.7 ± 0.4	0.9 ± 0.6	0.7 ± 0.6	0.8 ± 0.4	0.6 ± 0.5	0.6 ± 0.4
Cr:Crn Ratio	0.89 ± 0.73	2.13 ± 1.97†	0.88 ± 0.38	3.46 ± 2.25†	0.82 ± 0.75	0.53 ± 0.37	0.63 ± 0.25	0.43 ± 0.44

Results are mean ± SD. * Indicates a main effect for gender ($P < 0.05$). † Indicates a significant group x time interaction with the creatine group showing an increase after training ($P < 0.05$).

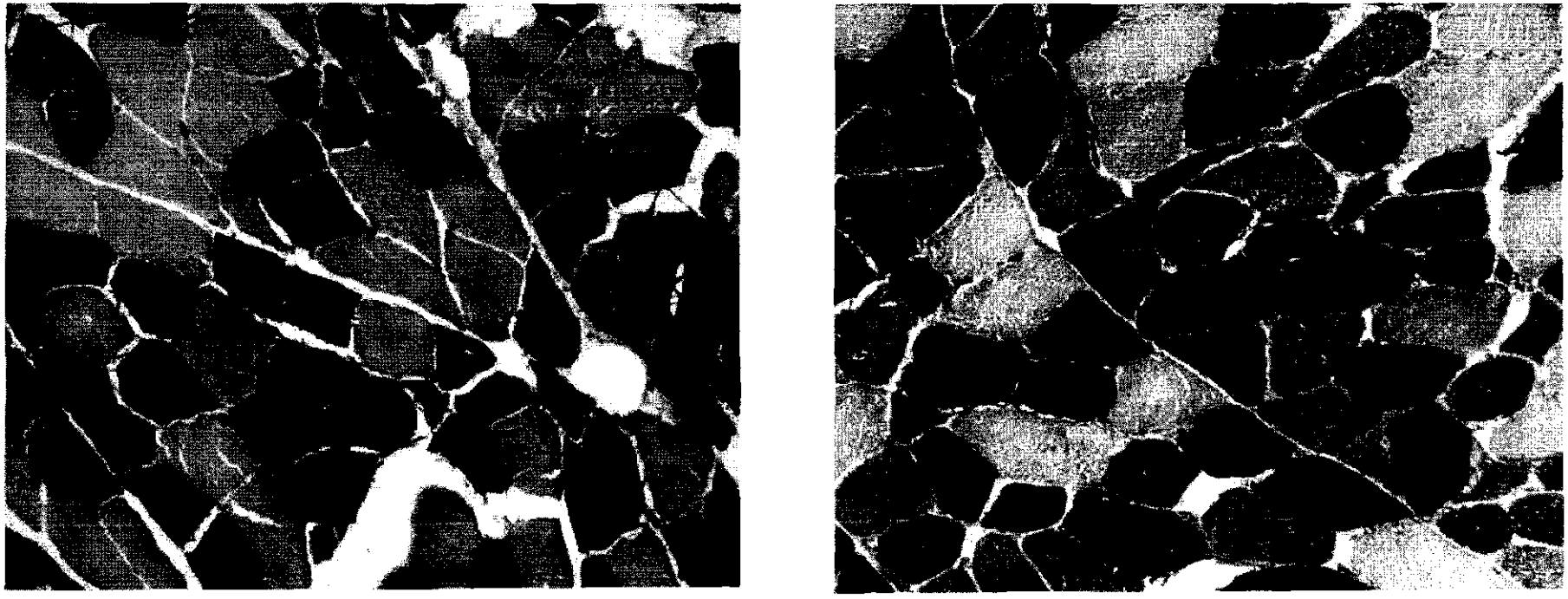


Figure 1. A representative histochemical stain, pre- and post- training (ph 4.48).

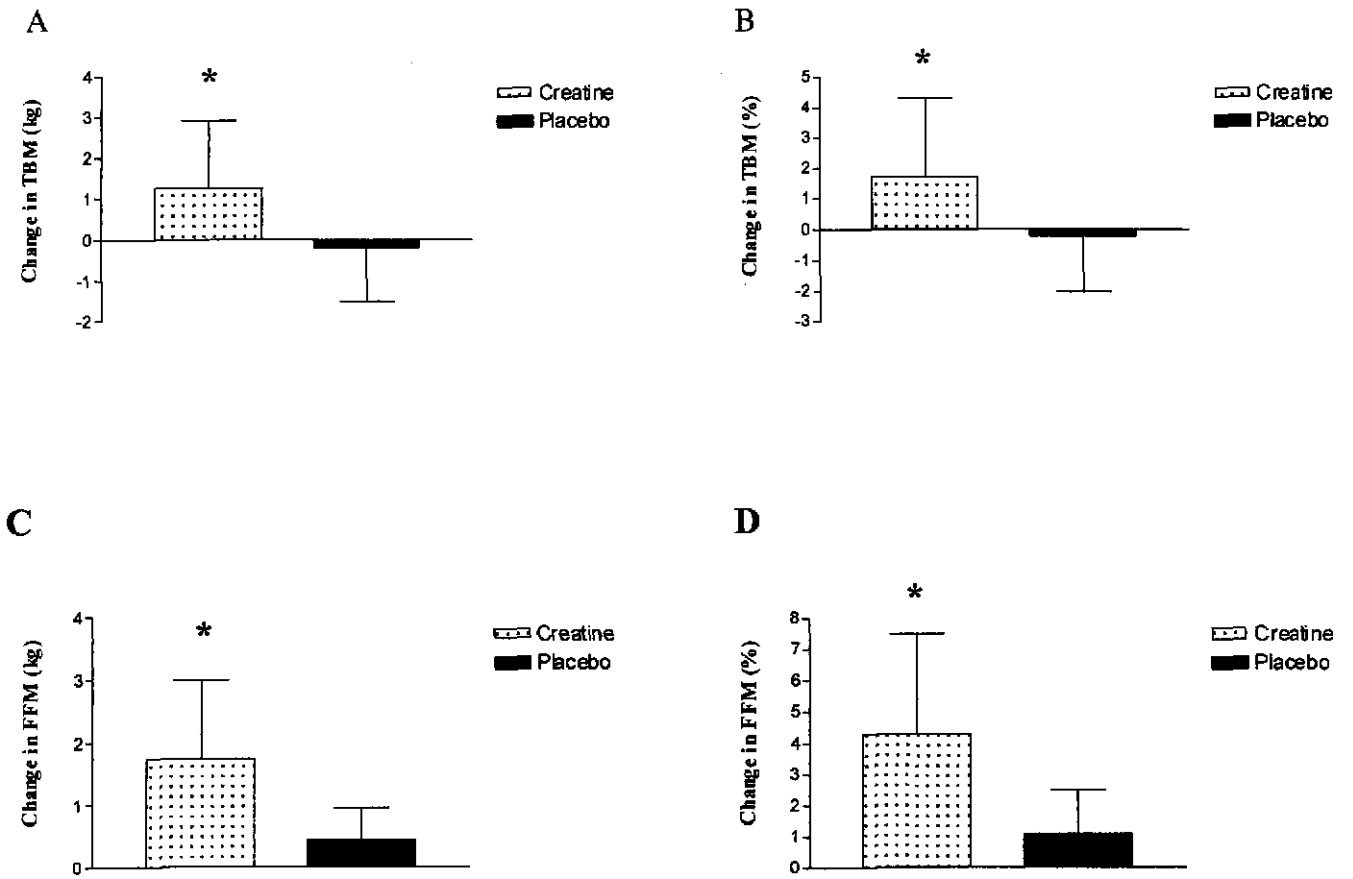


Figure 2. Absolute and relative changes in TBM (A and B) and FFM (C and D) for creatine vs. placebo after 14 weeks of resistance training. * Indicates a significant difference between groups, and pre- to post-treatment within a group ($p<0.05$).

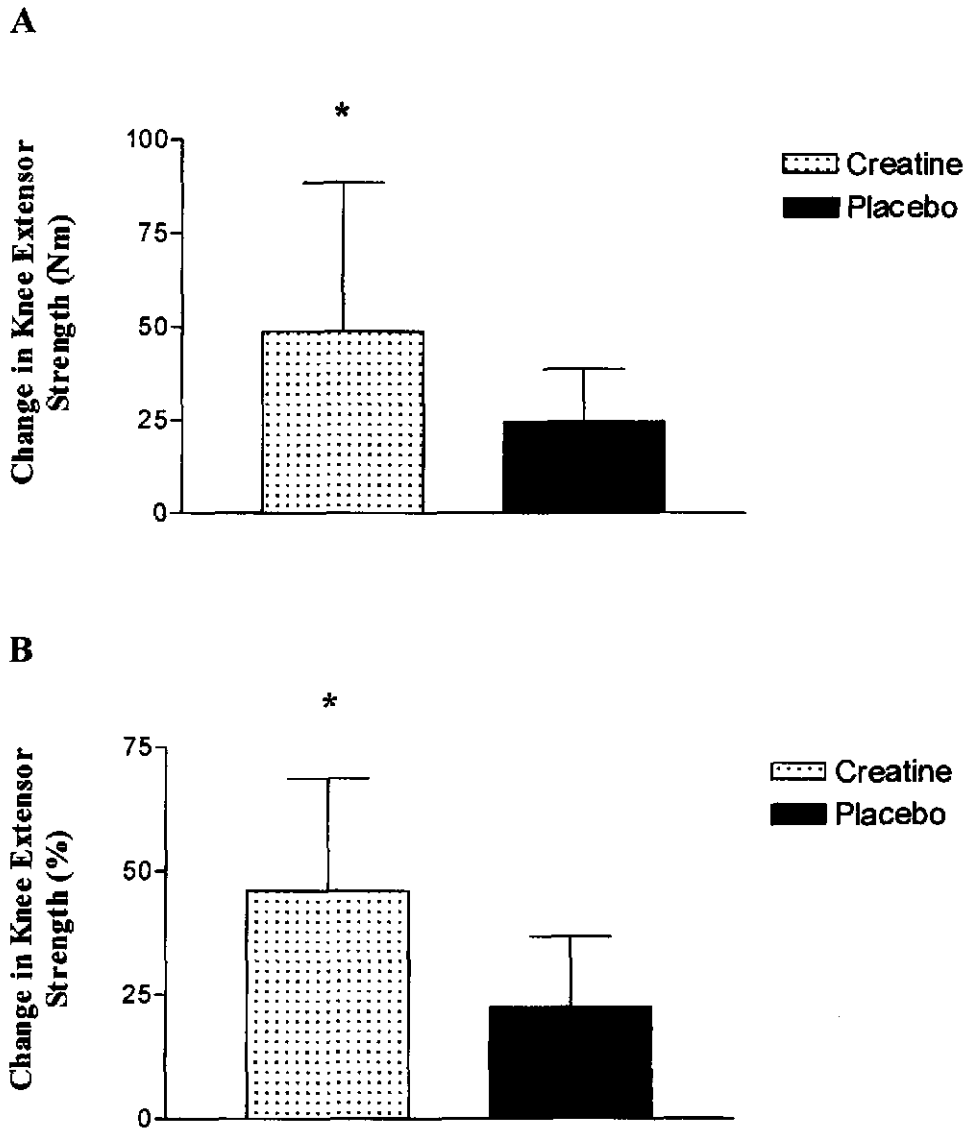


Figure 3. Absolute (A) and relative (B) change in knee extensor strength for creatine vs. placebo after 14 weeks of resistance training. * Indicates a significant difference between groups, and pre- to post-treatment within a group ($p<0.05$).

Discussion

The current study demonstrated that 14 weeks of resistance training improved muscle strength, fiber area, and performance on functional tasks in healthy, community- dwelling, older adults. In addition, CrM supplementation resulted in further gains in TBM, LBM, and isometric knee extension strength in both men and women and isometric dorsiflexion strength in men only. The importance of these findings are emphasized by the fact that the age-related losses in strength, and hence, physical functioning, lead to a loss of independence. The ability of older adults to reverse these losses in strength and function, and further, the ability of creatine monohydrate supplementation to enhance these reversals, is significant as this may preserve the independence and quality of life in older adults. Moreover, the prolonging of an independent lifestyle in an aging population may substantially reduce the financialburden on the health care system associated with caring for dependent older adults.

The results of the current study confirm that 14 weeks of whole body resistance training can significantly improve both isometric and dynamic measures of muscle strength. There was a marked improvement in strength for all exercises, with the exception of isometric handgrip strength, ranging from 26 to 60% (Table 4). The improvements in muscle strength are consistent with the results reported by others where subjects were trained under similar conditions (Brown et al., 1990; Charette et al., 1991; Hunter et al., 1995; Pyka et al., 1994). In addition, no injuries were reported during training or testing which reinforces

the idea that intense resistance training is a safe and effective method for strength development in older adults.

The strength improvements reported in the present study may have profound effects on the quality of life in older adults. It has previously been shown that maintenance of lower body muscle strength is correlated with a reduction in the prevalence of falls and associated fractures (Guralnik et al., 1995; Province et al., 1995). Moreover, a decline in lower body strength, especially knee extensor strength, is associated with decrements in walking speed, stair climbing, and rising from a chair (Bassey et al., 1992; Fiatarone et al., 1990). Also, nursing home residents with a history of falls demonstrated significantly lower dynamic strength measurements of the knees and ankles when compared to nonfallers (Whipple et al., 1987). Accordingly, resistance training has been consistently shown to improve lower extremity strength and is associated with improvements in mobility skills, gait speed, falls efficacy, and chair rise performance in older adults (Fiatarone et al., 1994; Hunter et al., 1995; Schlicht et al., 2001). Thus, an intervention that increases strength and power will help in the prevention of falls and the maintenance of an independent lifestyle.

In the current study we have demonstrated that older adults, who did not have any functional limitations at the beginning of the study, improved measures of physical function following resistance training. Our data supports the existing literature which demonstrates that older individuals can improve their performance on a timed walk test as a result of resistance training (Hunter et al., 1995; Schlicht et al., 2001; Skeleton et al., 1995). We reported an 11% improvement in walking speed which is consistent with

findings reported by Hunter and colleagues (1995) and Schlicht and colleagues (2001). We also reported a significant improvement in the 30-second chair stand, a test that is thought to reflect lower body strength. Other studies evaluating the effect of resistance training on sit to stand performance have reported mixed findings. One study reported a decrease in the time it took to complete 5 chair rises (Taaffe et al., 1999), while other studies have reported no changes in sit to stand performance (Schlicht et al., 2001; Skelton et al., 1995). However, methodological discrepancies may explain the equivocal findings cited in the literature. The test employed in the current study was a closed-ended time trial in which the subjects completed a required number of seconds rather than a required number of stands which is routinely used (Rikli and Jones, 1999). The latter protocol may be inadequate as a portion of older adults are unable to complete the required 5 or 10 stands (Guralnik et al., 1994). Lastly, we observed a significant improvement (24%) in the time to climb 14 stairs. Our findings are similar to those of Rooks and colleagues (1997) who reported an improvement in walking up a flight of stairs in community dwelling subjects (72 years) following 10 months of resistance training.

Chronic CrM supplementation has been shown to further enhance muscle strength gains (Vandenberghe et al., 1997) and total lifting volume (Kreider et al., 1998; Volek et al., 1999) in healthy young men and women. Kreider and colleagues (1998) reported that 28 days of resistance training in conjunction with CrM supplementation resulted in a greater increase in total lifting volume than the same training protocol without CrM supplementation in healthy young men. Similarly, Volek and colleagues (1999) found

that 12 weeks of resistance training combined with CrM supplementation resulted in a greater lifting volume in the bench press as compared to placebo. Furthermore, a study with healthy young females reported that 10 weeks of resistance training combined with CrM supplementation resulted in greater increases in muscle strength as compared to resistance training without CrM supplementation (Vandenberghe et al., 1997).

Although resistance training is a widely accepted method of improving strength among the elderly, only one study has investigated the ability of CrM supplementation and resistance training to further enhance strength gains in the elderly. However, this study failed to report any additional benefits of CrM supplementation with regards to further improving muscle strength (Bermon et al., 1998). In the present investigation, we found that chronic CrM supplementation (5g/d) differentially affected improvements in isometric strength. Supplementation with CrM further augmented gains in isometric knee extensor strength by 24% in both men and women and dorsiflexion strength by 15% in the men following resistance training but did not affect maximal isometric handgrip strength. This may be due to the increased sensitivity of measuring strength using custom made equipment. The test-retest reliability for our custom made equipment is less than for weight machines (0.5% vs. 5.0%). In addition, the measurement of isometric strength using a custom made device controls for extraneous variables (ie. measuring the strength of only the muscle group of interest, no indirect use of other muscle groups) better than weight machines. These observations are in agreement with findings of Urbanski and colleagues (1999), who reported that CrM supplementation increased maximal strength during isometric knee extension but not during handgrip

exercise in young men. This suggests that improvements in maximal strength following creatine supplementation may be restricted to movements performed with a large muscle mass.

Previously, resistance exercise training in the elderly has rendered conflicting results with respect to FFM. While some studies have reported significant increases in FFM following resistance training (Hunter et al., 2000; Taaffee et al., 1999; Treuth et al., 1994), whereas others have reported no increase in FFM (Ades et al., 1996; Bermon et al., 1998). The lack of consistent findings in these studies may be influenced by the intensity and duration of exercise, as well as the precision of measurement. Studies reporting no change in FFM following resistance training have often used skinfolds (Bermon et al., 1998) and hydrodensitometry (Ades et al., 1996) to estimate muscle mass. It is possible that these techniques are not sensitive enough to detect subtle changes in body composition following resistance training (Lohman, 1981). In contrast, studies using more sensitive measures to determine body composition such as DEXA (Nichols et al., 1993; Taaffe et al., 1999; Treuth et al., 1994), magnetic resonance imaging (Hurley et al., 1991), and computerized tomography (Brown et al., 1990; Fiatarone et al., 1990; Frontera et al., 1988), have consistently reported an increase in FFM following resistance exercise training. In the present study, we were unable to detect any changes in FFM in the placebo group, as determined by DEXA, following resistance exercise training. This highlights the importance of a more direct determination of FFM using site specific measurements such as MRI and CT and muscle biopsies to determine changes in muscle morphology.

A limited number of studies have investigated the potential benefits of CrM supplementation on body composition in older adults (Rawson and Clarkson, 1999; Rawson et al., 1999; Bermon et al., 1998). Most of these studies have been carried out in men and have generated equivocal findings. The choice of methodology may have contributed to this variability and has limited the interpretation of this research. Rawson and colleagues (1999) reported that 30 days of CrM supplementation (20g/d for 10 days followed by 4g/d for 20 days) did not affect body composition as determined by hydrostatic weighing. However, it should be noted that residual lung volume was determined from age and height estimations based on regression equations from young men and not by direct methods such as helium dilution. In addition, Bermon and colleagues (1998) found that 8 weeks of CrM supplementation (20 g/d for 5 days followed by 3 g/d for 47 days) with or without resistance training did not alter body composition as determined by anthropometry.

In the present study, strength training in conjunction with CrM supplementation induced significantly greater increases in TBM (1.2 ± 1.7 kg) and FFM (1.7 ± 1.2 kg) as compared to strength training while supplementing with PL (Table 2). The increase in TBM and FFM following chronic CrM supplementation combined with resistance training is comparable with findings of other studies in young men (Kreider et al., 1998; Volek et al., 1999) and women (Vandenberghe et al., 1997). The underlying mechanisms responsible for the increase in TBM remain to be elucidated. It has been suggested that the increase in TBM may be due to increased water retention (Hultman et al., 1996; Ziegenfuss et al., 1998). In addition, a creatine-stimulated increase in protein synthesis

has been suggested (Ingwall, 1976). Finally, Parise and colleagues (2001) have reported that short-term CrM supplementation results in a reduced rate of whole-body leucine oxidation and protein breakdown suggesting an anti-catabolic role for creatine.

Following resistance exercise training, significant increases in type I (Brown et al., 1990; Frontera et al., 1988; Pyka et al., 1994) and type II (Brown et al., 1990; Charette et al., 1991; Frontera et al., 1988; Pyka et al., 1994) muscle fiber area have been consistently reported in the literature. More recently, type IIa and IIx muscle fiber areas have been reported to increase following resistance exercise in the elderly (Hakkinen et al., 1998; Hikida et al., 2000). Similarly, a 13% and 31% increase in type I and type IIx muscle fiber area was reported in the present study.

Although we found a significant increase in muscle fiber area following training, we did not observe any effect of CrM supplementation. An early study by Sipilä and colleagues (1981) provided evidence supporting creatine as a potential anabolic agent. Creatine supplementation for 1 yr (1.5 g/d) in patients suffering from gyrate atrophy resulted in a significant increase in type II fiber diameter. More recently, Volek and colleagues (1999) found that CrM supplementation further increased muscle fiber area of all three fiber types following resistance training. However, in that study the CrM group started with a smaller mean fiber area prior to training as compared to the placebo group. Therefore, further experiments are needed to elucidate the link between creatine supplementation and body composition.

It has been hypothesized that adaptations in body composition and strength due to resistance training may be related to changes in anabolic hormone levels. Several studies

have examined the effects of resistance training on basal levels of hormones (Häkkinen and Pakarinen, 1994; Häkkinen et al., 2000; Nicklas et al., 1995). No changes in basal levels of TT, IGF-1, and DHEAS concentration were observed in the present study. These findings are in agreement with prior studies which have also failed to report changes in the basal concentrations of TT (Häkkinen and Pakarinen, 1994; Häkkinen et al., 2000; Izquierdo et al., 2001), IGF-1 (Nicklas et al., 1995), and DHEAS (Häkkinen et al., 2000) following resistance training. In general, the results obtained from the present study and other studies indicate that resistance training an older population does not lead to apparent changes in the basal concentrations of anabolic hormones.

Early work involving CrM supplementation suggested that those with lower intramuscular TCr levels stood to gain the most from CrM supplementation (Harris et al., 1992). In general, the lower the initial intramuscular TCr, the greater the creatine uptake into muscle (Gordon et al., 1995; Harris et al., 1992; Casey et al., 1996). More recently, we and others have reported that healthy elderly men and women (58-75 years) have significantly lower PCr and TCr concentrations as compared to young healthy men and women (19-30 years) (Campbell et al., 1999; Smith et al., 1998). Thus, it is possible, that these individuals may be at a disadvantage in activities requiring rapid energy turnover rates. Given the observed reductions in TCr and PCr in older adults (Campbell et al., 1999; Smith et al., 1998), it may be possible for CrM supplementation to optimize the availability of high-energy phosphates in those individuals whose intramuscular TCr levels are lower than normal.

This is the first study that has directly examined by muscle biopsy the capacity of older adults to creatine load. As hypothesized, CrM supplementation increased muscle TCr in males and females by an average of 26% which is in agreement with previous findings in young men (Balsom et al., 1995; Harris et al., 1992; Greenhaff et al., 1994). Traditionally, long term CrM supplementation at a lower dosage is often preceded by short term high dose loading (20-25g/d for 4-5 days). However, a novel finding of the present study was that the older subjects in the current study were able to increase TCr stores by ingestion of only 5g/d with no initial loading period.

One other study has examined basal concentrations of muscle PCr and PCr resynthesis rates in middle aged (58 ± 4.4 years) males and females before and after creatine supplementation using ^{31}P-MNR (Smith et al., 1998). Smith and colleagues (1998) reported that resting muscle PCr was lower in the middle-aged subjects as compared to the younger subjects. Following CrM supplementation, middle-aged subjects experienced a greater increase (30%) in muscle PCr stores as compared to younger subjects (15%); however, there was a similar improvement of repeated knee extension endurance for both groups.

The majority of studies examining the effect of CrM supplementation on performance and body composition have been carried out in men, although it appears that women can respond favourably to CrM supplementation. Mihic and colleagues (2000) reported that five days of CrM supplementation increased FFM in both males and females, however, the males experienced a greater increase in FFM. In contrast, we reported that males and females experienced equivalent gains in TBM and FFM.

Furthermore, Parise and colleagues (2001) reported that muscle TCr and PCr increased similarly in males and females following short-term CrM supplementation. In addition, Vandenberghe and colleagues (1997) reported improvements in muscle strength, increased TBM and FFM, and increased PCr in healthy young women supplemented with CrM for 10 weeks. Thus, there appears to be no concrete evidence of a gender specific effect in the responsiveness of muscle TCr and PCr to CrM supplementation.

The majority of studies have not reported any adverse side effects resulting from short-term (Juhn and Tarnopolsky, 1998; Mihic et al., 2000; Poortmans et al., 1997; Robinson et al., 2000) or long-term (Poortmans et al., 1999; Robinson et al., 2000) CrM supplementation upon haematological indices and indices of renal function. We found that the CrM supplement was well tolerated by the subjects with only minor abdominal discomfort reported in one male subject. In addition, one female in the PL group reported minor abdominal discomfort, including diarrhea. Plasma Crn concentration and CK activity increased to a greater extent for the CrM supplemented group following training. However, the observed increases in plasma Crn and CK activity remained within the normal limits for an older population. In addition, urine creatine, but not urine Crn, increased following CrM supplementation. We did not complete full 24-hour urine collections, however previous findings have reported no changes in Crn clearance or renal stress in response to CrM supplementation (Parise et al., 2001). The liver enzyme GGT also did not change in response to CrM supplementation. This is in agreement with studies which report no change in liver enzymes following CrM supplementation (Almada et al., 1996; Kamber et al., 1999). The present data suggest that there is no

obvious health risk following CrM supplementation at a dose of 5g/d for 4 months. Longer term studies will be required to better validate the initial greater gains in knee extensor strength, TBM and FFM and to determine whether these gains are maintained over time. Even if the improvements in strength and FFM are not maintained, CrM may still be of use in older adults or adults undergoing rehabilitation initiating a weight training program when compliance issues may be an issue.

In summary, 14 weeks of resistance training resulted in significant improvements in muscle strength and performance on functional tasks. In addition, there was a greater increase in FFM, TBM and knee isometric strength in those who supplemented with CrM. Although the mechanisms of these improvements remain to be elucidated, our results represent the first line of evidence suggesting that CrM supplementation may be beneficial in older adults.

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APPENDICES

APPENDIX A

Information and Consent

Letter of Information

Effect of creatine monohydrate and strength training upon muscle strength, muscle mass, protein metabolism and daily activity function in persons aged 65 – 80.

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Dept. of Kinesiology[$], McMaster University

This is an information letter to provide you with information regarding the above project. It is important that you read this letter in it's entirety and please feel free to ask any questions. After reading this and asking any questions, please read the accompanying consent form and sign it if you are willing to participate in the trial.

Creatine monohydrate (CM) is a natural substance found in meat and fish and is produced normally by the liver. CM is used commonly by athletes and increases muscle power by about 4% in healthy people. Studies in our laboratory have also shown an increase in lean body mass (mostly muscle) in men and women with creatine supplementation. Recently, in a smaller study, we demonstrated that short-term creatine supplementation increased muscle strength by 4 – 19 % in patients with a variety of neuromuscular diseases. We have found that with aging there is a reduction in muscle creatine content that is similar to that seen in muscular dystrophy. This may be a factor in the muscle shrinking and weakness that accompanies the aging process. Preliminary studies have shown that creatine is well tolerated in persons over the age of 65 y and that there is a slight increase in strength. In the current study we plan to investigate the effects of creatine and strength training upon muscle function, muscle size and mass, muscle creatine stores and functional activities in persons between the ages of 65 and 80 y.

You will be randomly chosen to receive either creatine (5 gm/day) or a sugar placebo for the entire 4 month exercise training period. Neither you, nor the study investigators, will be aware of the allocation of creatine vs. placebo until after the study is completed. All participants will receive the benefits of the strength training, yet half will receive creatine and half a sugar placebo.

We will be studying males and females between the ages of 65 – 80 who are relatively healthy and would like to participate in an exercise training (weight training) program. All persons must not have diabetes, uncontrolled high blood pressure, unstable angina, kidney failure nor any other medical condition that could be made worse by participation in the trial.

There will be two testing sessions (before and after the 4 month exercise training): These will take place at McMaster University Medical Center and at the Ivor Wynne Center and in total will take about 60 minutes. We will be calling you to arrange a schedule for your testing with exact dates and times. The testing methods are outlined below:

. Neuromuscular function (McMaster Hospital): This requires you to grip a device to measure hand strength, lift up your foot and extend your knee to measure leg strength.
2. DEXA Scan (McMaster hospital): this is a device that measures the amount of fat and muscle that you have in your body – It is a very low level X-ray type device that gives a low dose of radiation (see consent form).
3. BLOOD (McMaster hospital): About 15 mL (1 tablespoon) of blood will be taken to look at muscle enzymes, nutritional status, and a creatine breakdown product.
4. MUSCLE BIOPSY MEASUREMENTS (McMaster hospital): These are required to look at the size of individual muscle fibers and to see how much creatine gets into the muscle. This will be taken from the outside of the thigh using a hollow needle before and after the 4 months of exercise training. The amount of muscle is about 1/10,000 th of the muscle mass (needle is about the size of a small pencil) and does not impair function (Please see consent form for more details).
5. Muscle strength (Ivor Wynne Centre): You will be required to perform your maximal strength performance on 5 different exercises (knee extension, leg press, arm (biceps curl), bench press and triceps (arm) press-down.

You will be required to come in 3 times per week for a total of 4 months and perform resistance (weights) exercise. This type of exercise has been shown to significantly increase the strength of the muscles, which may allow you to feel stronger in your daily activities. Each session will take about one hour of your time and you will have supervision by a trainer to ensure that you are performing the exercises safely.

We thank you for your interest in the study. Please keep this form and do not hesitate to call any of us if you require any further information.
One of us will always be available during the study:

Dr. Tarnopolsky 521-2100 (75226) or pager 76443- # 2888
Andrea Brose 521-2100 (76452) or 525-9140 (27390)
Gianni Parise 521-9140 (27390 or 22427)

- CONSENT FORM IS ATTACHED
- PLEASE KEEP THIS FORM AND A COPY OF THE CONSENT FORM (BELOW) WITH YOU FOR FUTURE REFERENCE.

CONSENT FORM

Effect of creatine monohydrate and strength training upon muscle strength, muscle mass, protein metabolism and daily activity function in persons aged 65 – 80.

Dr. M. Tarnopolsky[+], MD, PhD, FRCP(C)
Dr. J. Bourgeois[*], MD, FRCP(C)
Dr. N. McCartney[$], PhD
Dept. of Medicine[+], McMaster University
Dept. of Pathology[*], McMaster University
Dept. of Kinesiology[$], McMaster University

The purpose and outline of the above study is contained in the affixed information sheet and it is important o carefully read that form and ask any questions as required.

The signing of this form indicates that you are willing to participate in the creatine and muscle strength raining study as indicated above. You will receive a copy of this signed consent form.

You are free to withdraw from the study at any time, and this will not impact upon your medical care whatsoever.

All data will be treated as being confidential and you will not be identified in any of the resulting presentations and papers. You will have access to your own data and the group data when it is available, for your own interest.

There are potential side effects associated with any intervention. We have had much experience with similar studies and will take every measure to ensure your comfort and safety. The potential side effects will be outlined below:

- Creatine has been used by millions of athletes throughout the world for over 5 years. There is one report of an individual with pre-existing renal disease who showed an apparent worsening of kidney function while supplementing and another report of interstitial nephritis in a young man taking twice the recommended maximal dose for 1 month. Because of these case reports we will be conservative and exclude those with known or the potential for (i.e., diabetes) kidney disease. There have been 2 longitudinal studies using creatine for > 1 month and neither has shown any significant adverse effects. All blinded trials that have measured renal function have not shown any deterioration. There have been some anecdotal reports of stomach cramps, however, this appears to be related to the consumption of un-dissolved powder in a minority of subjects.
- Muscle Testing: Muscle strength testing may pose some risk for ligamentous or tendon injury. Knee extension strength is a standard testing and training method used in most patients with lower extremity surgery rehabilitation. Any reports of tendon/ligament pain will be assessed by one of the supervising physicians and appropriate external consultation sought if it does not resolve with minor interventions.
- DEXA Scan: A DEXA scan is the most accurate measurement of body fat mass currently available. It uses a very low intensity radioactive beam to measure the amount of muscle and fat. The amount of radiation exposure is less than a cross-Canada airplane flight and much less than a standard chest X-ray (> 10 X less). There are no known risks with this test.
- Blood sampling. A single needle stick (Venipuncture) will be used to take blood twice during the study (pre-and post-exercise training). The possibility of a small bruise at the site exists. The total amount of blood taken at any time is going to be 15 ml, which should have no negative effects.

- Strength training. Strength training has been completed successfully in persons up to the age of 90 y. There is always the risk of injury to a joint, ligament or tendon even in a person in their thirties. You will be supervised and asked to report any unusual symptoms of muscle or joint pain to the trainer. Some people can have underlying cardiovascular disease and the stress of exercise could induce a heart attack or even sudden death. This risk is very low, as even patients following bypass, heart attack and heart transplant have successfully completed this type of training. If you experience any shortness of breath, chest pain, dizziness or other bothersome symptom, please report it to the trainer and/or call one of the coordinators.

- Muscle biopsy. A muscle biopsy will be taken using a small hollow needle from the outer leg muscle. He has performed over 9,000 of these in patients and healthy control subjects ranging in age from 1 week to 90 y. with the following complications:
  - 4/9,000 with a local skin infection.
  - 6/9,000 with a fibrous lump at the site of biopsy (connective tissue); all disappeared with massage after < 1 week.
  - 4/9,000 with a small patch of numbness just past the biopsy incision (size of a quarter) due to cutting a small sensory nerve branch. In all cases complete recovery occurred in < 3 months.
  - The muscle usually has a dull ache for 24-48 h (markedly reduced with ice and mild analgesics such as Tylenol or Advil).
  - In theory, one could damage a small motor branch of the m. *vastus lateralis* and partially weaken the lower aspect of the muscle. This should not affect function for this muscle is only one of the four that have a role in knee extension. However, it has not been observed in any of the patients biopsied by Dr. Tarnopolsky.

You will receive an honorarium of $ 100.00 for the completion of the study to help compensate for your time commitment. You are free to withdraw from the study at any time but may forfeit part or all of the honorarium. If you drop out due to an injury or for any reason directly related to the study itself you will be compensated for the entire study; if you drop out before the end of the study for personal reasons (injury, illness, etc.) then you will be compensated for the proportion that you completed.

If, after reading the above information, you are interested in participating as a subject please read the tatement below and sign in the space provided.

have read and understand the above explanation of the purpose and procedures of the project, and agree to articipate as a subject. I have received a copy of this form. I will contact Dr. Mark Tarnopolsky if I have a uestion about the study and know that he will be available on a 24 h basis during the duration of the study.

)r. Mark Tarnopolsky- (905) 521-1200 (x75226 or 76593 or x76443 pager 2888).
)r. Jackie Bourgeois- (905) 521-2100 (76314)
)r. N. McCartney – (905) 525-9140 (X 24469)

lame	Signature	Date
/itness (Name)	Signature	Date

APPENDIX B

Statistical Summary Tables

ANOVA table 1: Age

	df Effect	MS Effect	df Error	MS Error	F	p-level
Group	1	17.49853	24	28.49405	0.614112	0.44091
Gender	1	18.29381	24	28.49405	0.642022	0.430841
Group x Gender	1	2.706186	24	28.49405	0.094974	0.760606

ANOVA table 2: Height

	df Effect	MS Effect	df Error	MS Error	F	p-level
Group	1	13.09794	24	42.44122	0.308614	0.583674
Group x Gender	1	42.68262	24	42.44122	1.005688	0.325943

ANOVA table 3: Total Body Mass

	df Effect	MS Effect	df Error	MS Error	F	p-level
Group	1	225.218	24	363.6745	0.619285	0.439016
Group x Gender	1	265.1521	24	363.6745	0.729092	0.40162
Gender x Time	1	0.031615	24	1.191105	0.026543	0.871945
Group x Gender x Time	1	0.384193	24	1.191105	0.322552	0.575354

ANOVA table 4: Fat Free Mass

	df Effect	MS Effect	df Error	MS Error	F	p-level
Group	1	5808447	12	51532844	0.112713	0.742873
Gender	1	96389120	12	51532844	1.87044	0.196493
Group x Gender	1	96389120	12	51532844	1.87044	0.196493
Time	1	398615.6	12	603980.9	0.65998	0.432388
Gender x Time	1	398615.6	12	603980.9	0.65998	0.432388
Group x Gender x Time	1	1631.38	12	603980.9	0.002701	0.959406

ANOVA table 5: Fat Mass

	df Effect	MS Effect	df Error	MS Error	F	p-level
Group	1	48431280	12	1.62E+08	0.29983	0.594027
Gender	1	1.44E+08	12	1.62E+08	0.89085	0.363863
Time	1	7652235	12	8468889	0.90357	0.360579
Group x Gender	1	3.73E+08	12	1.62E+08	2.311757	0.154302
Group x Time	1	4712003	12	8468889	0.55639	0.470079
Gender x Time	1	9426708	12	8468889	1.113099	0.312189
Group x Gender x Time	1	7761627	12	8468889	0.916487	0.35729

ANOVA table 6: % Body Fat

	df Effect	MS Effect	df Error	MS Error	F	p-level
Group	1	108.1273	12	161.0454	0.671409	0.428535
Gender	1	4.620696	12	1.440833	3.20696	0.098564
Time	1	4.620696	12	1.440833	3.20696	0.098564
Group x Gender	1	156.7914	12	161.0454	0.973585	0.343266
Group x Time	1	0.488522	12	1.440833	0.339055	0.571154
Gender x Time	1	2.894087	12	1.440833	2.00862	0.181845
Group x Gender x Time	1	0.605391	12	1.440833	0.420167	0.529062

ANOVA table 7: Kcal/d

	df Effect	MS Effect	df Error	MS Error	F	p-level
Group	1	125051.3	24	349619.3	0.357679	0.555401
Time	1	150700.4	24	145563.3	1.035291	0.319067
Group x Gender	1	85437.14	24	349619.3	0.244372	0.625561
Group x Time	1	59177.19	24	145563.3	0.406539	0.529768
Gender x Time	1	966.6719	24	145563.3	0.006641	0.935727
Group x Gender x Time	1	182317.7	24	145563.3	1.252497	0.274152

ANOVA table 8: %CHO

	df Effect	MS Effect	df Error	MS Error	F	p-level
Group	1	434.4676	24	113.1353	3.840248	0.061749
Gender	1	19.78427	24	113.1353	0.174873	0.679535
Time	1	2.187316	24	38.67299	0.056559	0.814038
Group x Gender	1	2.320355	24	113.1353	0.02051	0.887319
Group x Time	1	14.99144	24	38.67299	0.387646	0.539411
Gender x Time	1	35.58938	24	38.67299	0.920264	0.346971
Group x Gender x Time	1	0.022367	24	38.67299	0.000578	0.981012

ANOVA table 9: %FAT

	df Effect	MS Effect	df Error	MS Error	F	p-level
Group	1	17.39718	24	43.984	0.395534	0.535345
Gender	1	12.29409	24	43.984	0.279513	0.601876
Time	1	0.172588	24	14.54055	0.011869	0.91415
Group x Gender	1	26.02605	24	43.984	0.591716	0.449261
Group x Time	1	46.19321	24	14.54055	3.176854	0.087345
Gender x Time	1	10.07391	24	14.54055	0.692815	0.413415
Group x Gender x Time	1	6.98113	24	14.54055	0.480115	0.495021

ANOVA table 10: %PRO

	df Effect	MS Effect	df Error	MS Error	F	p-level
Group	1	5.107511	24	10.03571	0.508933	0.482481
Gender	1	0.159057	24	10.03571	0.015849	0.900865
Time	1	18.0972	24	7.636905	2.369704	0.136793
Group x Gender	1	2.138439	24	10.03571	0.213083	0.648518
Group x Time	1	0.282769	24	7.636905	0.037027	0.84903
Gender x Time	1	0.070692	24	7.636905	0.009257	0.924151
Group x Gender x Time	1	0.070692	24	7.636905	0.009257	0.924151

ANOVA table 11: PRO (g)

	df Effect	MS Effect	df Error	MS Error	F	p-level
Group	1	532.6938	24	668.5565	0.796782	0.38092
[redacted]						
Time	1	20.41703	24	273.7231	0.07459	0.787104
Group x Gender	1	27.36071	24	668.5565	0.040925	0.841388
Group x Time	1	32.35781	24	273.7231	0.118214	0.733974
Gender x Time	1	16.39277	24	273.7231	0.059888	0.808753
Group x Gender x Time	1	231.5194	24	273.7231	0.845816	0.366891

ANOVA table 12: Protein (g/kg/d)

	df Effect	MS Effect	df Error	MS Error	F	p-level
Group	1	146.1494	24	112.5625	1.298384	0.265754
Gender	1	146.541	24	112.5625	1.301863	0.265131
Time	1	159.0154	24	114.863	1.384392	0.250893
Group x Gender	1	164.6414	24	112.5625	1.462666	0.238286
Group x Time	1	158.8143	24	114.863	1.382641	0.251185
Gender x Time	1	157.3159	24	114.863	1.369596	0.253372
Group x Gender x Time	1	153.5372	24	114.863	1.336698	0.258997

ANOVA table 13: Phosphocreatine

	df Effect	MS Effect	df Error	MS Error	F	p-level
Group	1	75.75681	22	518.8481	0.14601	0.706044
Gender	1	290.1679	22	518.8481	0.559254	0.462481
Time	1	339.9146	22	322.7801	1.053084	0.315949
Group x Gender	1	281.6385	22	518.8481	0.542815	0.469053
Group x Time	1	1092.274	22	322.7801	3.383956	0.079368
Gender x Time	1	211.0098	22	322.7801	0.653726	0.427441
Group x Gender x Time	1	1384.341	22	322.7801	4.288806	0.050297

ANOVA table 14: Creatine

	df Effect	MS Effect	df Error	MS Error	F	p-level
Group	1	15.95313	22	439.2839	0.036316	0.850612
Gender	1	30.77012	22	439.2839	0.070046	0.793733
Time	1	1145.484	22	300.8508	3.807481	0.063873
Group x Gender	1	890.7291	22	439.2839	2.027684	0.168486
Group x Time	1	927.3513	22	300.8508	3.082429	0.093058
Gender x Time	1	122.1975	22	300.8508	0.406173	0.530496
Group x Gender x Time	1	9.602817	22	300.8508	0.031919	0.859841

ANOVA table 15: Total Creatine

	df Effect	MS Effect	df Error	MS Error	F	p-level
Group	1	22.18138	22	509.3301	0.04355	0.836613
Gender	1	509.9198	22	509.3301	1.001158	0.32791
Group x Gender	1	170.6421	22	509.3301	0.335032	0.56859
Gender x Time	1	12.05394	22	360.9472	0.033395	0.856673

ANOVA table 16: ATP

	df Effect	MS Effect	df Error	MS Error	F	p-level
Group	1	13.1936	22	20.22792	0.652247	0.427957
Gender	1	0.225089	22	20.22792	0.011128	0.916945
Time	1	11.45365	22	8.363051	1.369555	0.25441
Group x Gender	1	9.08213	22	20.22792	0.44899	0.509788
Group x Time	1	15.17944	22	8.363051	1.81506	0.191616
Gender x Time	1	17.43735	22	8.363051	2.085046	0.162839
Group x Gender x Time	1	11.38612	22	8.363051	1.36148	0.255774

ANOVA table 17: Max Isometric Knee Extensor Strength

	df Effect	MS Effect	df Error	MS Error	F	p-level
Group	1	2272.816	23	1352.533	1.680414	0.207726
Gender	1	243.1001	23	1352.533	0.179737	0.675538
Group x Gender	1	243.1001	23	1352.533	0.179737	0.675538
Time	1	827.8297	23	389.2263	2.126859	0.158259
Gender x Time	1	827.8297	23	389.2263	2.126859	0.158259
Group x Gender x Time	1	876.7512	23	389.2263	2.252548	0.146999

ANOVA table 18: Max Isometric Handgrip Strength

	df Effect	MS Effect	df Error	MS Error	F	p-level
Group	1	7112.381	24	7003.656	1.015524	0.323636
Gender	1	11976.77	24	7003.656	1.710074	0.203364
Time	1	1492.802	24	870.1275	1.715613	0.202659
Group x Gender	1	11976.77	24	7003.656	1.710074	0.203364
Group x Time	1	344.5797	24	870.1275	0.396011	0.535102
Gender x Time	1	1226.769	24	870.1275	1.409873	0.246697
Group x Gender x Time	1	511.1518	24	870.1275	0.587445	0.450883

ANOVA table 19: Max Isometric Dorsiflexion Strength

	df Effect	MS Effect	df Error	MS Error	F	p-level
Group	1	192.3483	24	200.687	0.958449	0.337344
Gender	1	67.55224	24	200.687	0.336605	0.567203
Time	1	26.80035	24	20.65977	1.297224	0.265962
Group x Gender	1	67.55224	24	200.687	0.336605	0.567203
Group x Time	1	26.80035	24	20.65977	1.297224	0.265962
Gender x Time	1	3.517733	24	20.65977	0.17027	0.683535
Group x Gender x Time	1	3.517733	24	20.65977	0.17027	0.683535

ANOVA table 20: 1 RM - Arm Flexion

	df Effect	MS Effect	df Error	MS Error	F	p-level
[illegible]						
Group x Time	1	69.40402	24	23.1245	3.00132	0.096031
[illegible]						
Group x Gender x Time	1	25.96956	24	23.1245	1.123032	0.299816

ANOVA table 21: 1RM - Seated Chest Press

	df Effect	MS Effect	df Error	MS Error	F	p-level
Group	1	2100.808	22	766.7067	2.740041	0.112059
[illegible]						
Group x Gender	1	1228.5	22	766.7067	1.602308	0.218818
Group x Time	1	67.51649	22	60.72403	1.111858	0.303122
[illegible]						
Group x Gender x Time	1	41.20879	22	60.72403	0.678624	0.418902

ANOVA table 22: 1RM - Knee Extension

	df Effect	MS Effect	df Error	MS Error	F	p-level
Group	1	283.8019	23	891.5321	0.318331	0.578074
[illegible]						
Group x Gender	1	601.6076	23	891.5321	0.674802	0.419816
Group x Time	1	0.007619	23	146.7992	5.19E-05	0.994314
Gender x Time	1	20.6019	23	146.7992	0.140341	0.711374
Group x Gender X Time	1	0.190476	23	146.7992	0.001298	0.971576

ANOVA table 23: 1RM - Leg Press

	df Effect	MS Effect	df Error	MS Error	F	p-level
Group	1	1937.385	22	2825.227	0.685745	0.416509
[illegible]						
Group x Gender	1	940.2422	22	2825.227	0.332802	0.56987
Group x Time	1	286.484	22	328.7852	0.871341	0.360717
Gender x Time	1	527.1653	22	328.7852	1.603373	0.21867
Group x Gender x Time	1	78.8576	22	328.7852	0.239845	0.629166

ANOVA table 24: Timed Walk Test

	df Effect	MS Effect	df Error	MS Error	F	p-level
Group	1	8.830061	24	9.550891	0.924527	0.345877
[redacted]						
Group x Gender	1	0.693118	24	9.550891	0.072571	0.789932
Group x Time	1	0.067893	24	1.855182	0.036596	0.849899
Gender x Time	1	0.007467	24	1.855182	0.004025	0.94994
Group x Gender x Time	1	0.025875	24	1.855182	0.013947	0.906972

ANOVA table 25: Timed Stair Climb

	df Effect	MS Effect	df Error	MS Error	F	p-level
Group	1	0.014648	24	3.184218	0.0046	0.946486
Gender	1	1.160364	24	3.184218	0.364411	0.55173
[redacted]						
Group x Gender	1	0.155149	24	3.184218	0.048725	0.827165
Group x Time	1	0.793047	24	0.788055	1.006334	0.32579
Gender x Time	1	0.197006	24	0.788055	0.24999	0.621636
Group x Gender x Time	1	1.258542	24	0.788055	1.597022	0.218463

ANOVA table 26: 30s Chair Stand Test

	df Effect	MS Effect	df Error	MS Error	F	p-level
Group	1	0.956633	16	70.41093	0.013586	0.908659
Gender	1	0.344388	16	70.41093	0.004891	0.945111
[redacted]						
Group x Gender	1	9.552551	16	70.41093	0.135669	0.717453
Group x Time	1	0.906292	16	5.515104	0.164329	0.69057
Gender x Time	1	19.31446	16	5.515104	3.502102	0.079691
Group x Gender x Time	1	0.718537	16	5.515104	0.130285	0.722858

ANOVA table 27: Type I Fiber Area

	df Effect	MS Effect	df Error	MS Error	F	p-level
Group	1	952935.4	24	2571316	0.370602	0.548396
[illegible]						
Group x Gender	1	399973.3	24	2571316	0.155552	0.696768
Group x Time	1	267940.5	24	835888	0.320546	0.576536
Gender x Time	1	1543026	24	835888	1.845972	0.186886
Group x Gender x Time	1	195744.2	24	835888	0.234175	0.632831

ANOVA table 28: Type IIa Fiber Area

	df Effect	MS Effect	df Error	MS Error	F	p-level
Group	1	2106595	24	2121563	0.992945	0.328965
[illegible]						
Time	1	3457549	24	1195122	2.893051	0.101886
Group x Gender	1	2722871	24	2121563	1.283427	0.268454
Group x Time	1	69066.89	24	1195122	0.057791	0.812064
Gender x Time	1	4142020	24	1195122	3.465771	0.074942
Group x Gender x Time	1	78319.02	24	1195122	0.065532	0.800138

ANOVA table 29: Type IIx Fiber Area

	df Effect	MS Effect	df Error	MS Error	F	p-level
Group	1	1676442	24	1720542	0.974369	0.333441
[illegible]						
Group x Gender	1	5219406	24	1720542	3.033583	0.094362
Group x Time	1	63573.25	24	1014606	0.062658	0.804473
Gender x Time	1	1159421	24	1014606	1.142731	0.29571
Group x Gender x Time	1	158885.2	24	1014606	0.156598	0.695804

ANOVA table 30: % Area - Type I

	df Effect	MS Effect	df Error	MS Error	F	p-level
Group	1	22.93609	24	366.1729	0.062637	0.804505
Time	1	6.262986	24	105.6029	0.059307	0.809664
Group x Gender	1	128.0636	24	366.1729	0.349735	0.559793
Group x Time	1	119.3413	24	105.6029	1.130095	0.298335
Gender x Time	1	14.17919	24	105.6029	0.134269	0.717257
Group x Gender X Time	1	0.695887	24	105.6029	0.00659	0.935975

ANOVA table 31: % Area - Type IIa

	df Effect	MS Effect	df Error	MS Error	F	p-level
Group	1	131.3693	24	144.213	0.91094	0.34938
Gender	1	325.84	24	144.213	2.259436	0.145848
Time	1	111.7215	24	64.58799	1.729757	0.20087
Group x Gender	1	33.62145	24	144.213	0.233137	0.633582
Group x Time	1	211.872	24	64.58799	3.280363	0.082649
Gender x Time	1	267.9918	24	64.58799	4.149252	0.052827
Group x Gender x Time	1	9.96171	24	64.58799	0.154235	0.697987

ANOVA table 32: % Area - Type IIx

	df Effect	MS Effect	df Error	MS Error	F	p-level
Group	1	28.88095	24	242.8607	0.11892	0.733213
Time	1	86.2272	24	110.8636	0.777778	0.386569
Group x Gender	1	250.1629	24	242.8607	1.030068	0.320266
Group x Time	1	5.319985	24	110.8636	0.047987	0.828456
Gender x Time	1	129.6481	24	110.8636	1.169438	0.290264
Group x Gender x Time	1	7.104609	24	110.8636	0.064084	0.802309

ANOVA table 33: % Distribution - Type I

	df Effect	MS Effect	df Error	MS Error	F	p-level
Group	1	42.95417	24	321.9429	0.133422	0.71811
Gender	1	1058.228	24	321.9429	3.287007	0.082358
Time	1	3.78872	24	80.78172	0.046901	0.830377
Group x Gender	1	18.66716	24	321.9429	0.057983	0.811758
Group x Time	1	126.9627	24	80.78172	1.571677	0.222039
Gender x Time	1	10.44292	24	80.78172	0.129273	0.722331
Group x Gender x Time	1	0.051577	24	80.78172	0.000638	0.98005

ANOVA table 34: % Distribution - Type IIa

	df Effect	MS Effect	df Error	MS Error	F	p-level
Group	1	65.45632	24	128.5942	0.509014	0.482446
Gender	1	41.72872	24	128.5942	0.324499	0.57421
Time	1	28.98822	24	91.15518	0.31801	0.578038
Group x Gender	1	67.95346	24	128.5942	0.528433	0.474298
Group x Time	1	273.9367	24	91.15518	3.005168	0.09583
[redacted]						
Group x Gender x Time	1	73.06905	24	91.15518	0.80159	0.379511

ANOVA table 35: % Distribution - Type IIx

	df Effect	MS Effect	df Error	MS Error	F	p-level
Group	1	215.8737	24	237.7163	0.908115	0.350115
Gender	1	682.02	24	237.7163	2.86905	0.103239
Time	1	12.25916	24	125.6791	0.097543	0.757495
Group x Gender	1	159.6532	24	237.7163	0.671612	0.420554
Group x Time	1	27.52204	24	125.6791	0.218987	0.644035
Gender x Time	1	297.9283	24	125.6791	2.370547	0.136726
Group x Gender x Time	1	69.78294	24	125.6791	0.555247	0.463417

ANOVA table 36: Total Testosterone

	df Effect	MS Effect	df Error	MS Error	F	p-level
Group	1	82722.73	23	45660.68	1.811684	0.191424
Gender						
Time	1	6054.51	23	9802.474	0.617651	0.439944
Group x Gender	1	98496	23	45660.68	2.15713	0.155455
Group x Time	1	10223.53	23	9802.474	1.042954	0.317758
Gender x Time	1	5549.388	23	9802.474	0.566121	0.459436
Group x Gender x Time	1	8685.988	23	9802.474	0.886102	0.356319

ANOVA table 37: DHEAS

	df Effect	MS Effect	df Error	MS Error	F	p-level
Group	1	3.265687	24	3.8179	0.855362	0.364246
Gender						
Time	1	1.295066	24	0.805307	1.608164	0.216914
Group x Gender	1	0.156385	24	3.8179	0.040961	0.841319
Group x Time	1	1.052915	24	0.805307	1.307471	0.264131
Gender x Time	1	0.06828	24	0.805307	0.084787	0.773414
Group x Gender x Time	1	0.046706	24	0.805307	0.057997	0.811735

ANOVA table 38: Insulin-like Growth Factor-1

	df Effect	MS Effect	df Error	MS Error	F	p-level
Group	1	44.52948	16	15.41189	2.889293	0.108524
Gender	1	19.63494	16	15.41189	1.274012	0.275656
Time	1	4.564164	16	2.434111	1.875085	0.189809
Group x Gender	1	0.017381	16	15.41189	0.001128	0.973626
Group x Time	1	0.025022	16	2.434111	0.01028	0.920502
Gender x Time	1	1.408905	16	2.434111	0.578817	0.457843
Group x Gender x Time	1	6.147102	16	2.434111	2.525399	0.131589

ANOVA table 39: Osteocalcin

	df Effect	MS Effect	df Error	MS Error	F	p-level
Group	1	30.6783	24	24.20793	1.267283	0.271409
Gender	1	51.85938	24	24.20793	2.142248	0.156267
Time	1	1.64585	24	2.834004	0.580751	0.453443
Group x Gender	1	2.574464	24	24.20793	0.106348	0.747167
Group x Time	1	0.320767	24	2.834004	0.113185	0.739471
Gender x Time	1	1.028304	24	2.834004	0.362845	0.55258
Group x Gender x Time	1	0.191011	24	2.834004	0.0674	0.797375

ANOVA table 40: GGT

	df Effect	MS Effect	df Error	MS Error	F	p-level
Group	1	65.77193	23	407.823	0.161276	0.691692
Gender	1	215.7719	23	407.823	0.529082	0.474333
Time	1	13.46582	23	14.76139	0.912233	0.349454
Group x Gender	1	872.6828	23	407.823	2.139857	0.157047
Group x Time	1	2.244696	23	14.76139	0.152065	0.700157
Gender x Time	1	17.92786	23	14.76139	1.214511	0.28184
Group x Gender x Time	1	2.376709	23	14.76139	0.161009	0.691933

ANOVA table 41: Creatine Kinase Activity

	df Effect	MS Effect	df Error	MS Error	F	p-level
Group	1	5014.742	24	5827.417	0.860543	0.362823
Gender	1	223.5261	24	5827.417	0.038358	0.846375
Time	1	3185.585	24	1224.087	2.602417	0.119774
Group x Gender	1	6370.363	24	5827.417	1.093171	0.306187
Group x Time	1	1677.001	24	1224.087	1.370001	0.253303
Gender x Time	1	33.84251	24	1224.087	0.027647	0.869334
Group x Gender x Time	1					

ANOVA table 42: Plasma Creatinine

	df Effect	MS Effect	df Error	MS Error	F	p-level
Group	1	2694.971	24	952.1452	2.83042	0.105461
Gender	1	1371.655	24	952.1452	1.440595	0.241757
Time	1	127.6521	24	313.9374	0.406616	0.529729
Group x Gender	1	127.2209	24	952.1452	0.133615	0.717915
Group x Time	1	44.07485	24	313.9374	0.140394	0.71118
Gender x Time	1	23.05452	24	313.9374	0.073437	0.788714
Group x Gender x Time	1					

ANOVA table 43: Urine Creatine

	df Effect	MS Effect	df Error	MS Error	F	p-level
Group						
Gender	1	1.978413	24	2.984901	0.662807	0.423575
Time						
Group x Gender	1	1.732281	24	2.984901	0.580348	0.453598
Group x Time						
Gender x Time	1	3.244217	24	2.201791	1.473445	0.236613
Group x Gender x Time	1	3.149145	24	2.201791	1.430265	0.243404

ANOVA table 44: Urine Creatinine

	df Effect	MS Effect	df Error	MS Error	F	p-level
Group	1	0.651609	24	0.371064	1.756054	0.197596
Gender	1	0.346115	24	0.371064	0.932762	0.343778
Time	1	0.113235	24	0.043692	2.591687	0.120502
Group x Gender	1	0.006057	24	0.371064	0.016323	0.899403
Group x Time	1	0.048188	24	0.043692	1.102905	0.30409
Gender x Time	1	0.010444	24	0.043692	0.239047	0.629334
Group x Gender x Time	1	0.000139	24	0.043692	0.003186	0.955455

APPENDIX C

Raw Data

Subject Characteristics - Age and Height

Subject	Group	Gender	Age (yr)	Height (cm)
1	Creatine	male	66	176
4	Creatine	male	67	169
11	Creatine	male	75	166
16	Creatine	male	73	163
17	Creatine	male	70	181.5
26	Creatine	male	60	174
30	Creatine	male	65	169
32	Creatine	male	70	177.5
	avg		**68.3**	**172.0**
	stdev		**4.8**	**6.3**
12	Creatine	female	65	170.5
19	Creatine	female	66	151
21	Creatine	female	68	160
22	Creatine	female	65	160
25	Creatine	female	81	161
27	Creatine	female	78	153
	avg		**70.5**	**159.3**
	stdev		**7.1**	**6.9**
2	Placebo	male	66	165.5
7	Placebo	male	64	170
10	Placebo	male	72	166
14	Placebo	male	68	170.5
15	Placebo	male	68	161.5
20	Placebo	male	70	166.5
23	Placebo	male	63	177
	avg		**67.3**	**168.1**
	stdev		**3.2**	**4.9**
3	Placebo	female	64	158
9	Placebo	female	72	157
13	Placebo	female	78	146
18	Placebo	female	72	170.5
24	Placebo	female	66	164
29	Placebo	female	61	163
31	Placebo	female	65	164
	avg		**68.3**	**160.4**
	stdev		**5.9**	**7.7**

Diet Analysis

Subject	Group	Gender	Kcal		%CHO		%PRO	
			Pre	Post	Pre	Post	Pre	Post
1	Creatine	male	2245	2858	48	49	20	16
4	Creatine	male	2337	2866	59	61	14	15
11	Creatine	male	1974	2191	48	51	18	18
16	Creatine	male	2643	2538	55	57	16	19
17	Creatine	male	3024	1529	58	59	13	17
26	Creatine	male	2039	2520	45	44	16	20
32	Creatine	male	1371	1233	56	55	16	19
30	Creatine	male	2360	2931	59	51	15	12
	avg		**2249**	**2333**	**54**	**53**	**16**	**17**
	stdev		**488**	**640**	**6**	**6**	**2**	**3**
12	Creatine	female	1881	1723	43	52	20	17
19	Creatine	female	1378	1346	55	56	12	17
21	Creatine	female	2012	1943	50	61	17	13
22	Creatine	female	2612	2125	51	52	12	16
25	Creatine	female	1490	1240	60	53	14	18
27	Creatine	female	1554	1578	43	46	18	18
	avg		**1821**	**1659**	**50**	**53**	**16**	**17**
	stdev		**457**	**341**	**7**	**5**	**3**	**2**
2	Placebo	male	1956	2077	45	42	17	15
7	Placebo	male	3067	3059	46	44	13	16
10	Placebo	male	1904	2135	54	44	18	18
14	Placebo	male	2200	2063	60	48	17	20
15	Placebo	male	2941	2318	42	52	19	15
20	Placebo	male	2742	2331	64	62	12	14
23	Placebo	male	3409	2304	29	32	17	23
	avg		**2603**	**2327**	**49**	**46**	**16**	**17**
	stdev		**587**	**343**	**12**	**9**	**3**	**3**
3	Placebo	female	1182	1283	20	48	15	17
9	Placebo	female	1468	1736	46	27	14	23
13	Placebo	female	1637	1929	55	54	20	15
18	Placebo	female	1903	974	52	44	15	19
31	Placebo	female	2033	2484	50	51	11	12
29	Placebo	female	1548	1788	56	57	22	17
24	Placebo	female	2747	1881	44	49	17	21
	avg		**1788**	**1725**	**46**	**47**	**16**	**18**
	stdev		**507**	**484**	**12**	**10**	**4**	**4**

Diet Analysis - continued

%FAT		PRO (g)		%OH		PRO (g/kg/d)	
Pre	Post	Pre	Post	Pre	Post	Pre	Post
32	33	112.5	116.1	0	2	1.64	1.63
21	18	84.6	111.8	6	5	0.87	1.14
33	30	89.2	102.8	1	1	1.24	1.43
25	23	108	118.7	4	1	1.54	1.64
27	24	106.1	66.7	1	0	1.02	0.64
38	35	81.1	127.01	1	0	0.83	1.31
28	26	54.77	61.2	0	0	0.63	0.68
25	37	92.7	88	3	0	1.21	1.109
29	**28**	**91.1**	**99.0**	**2**	**1**	**1.12**	**1.20**
5	**7**	**18.7**	**24.6**	**2**	**2**	**0.35**	**0.39**
38	31	94	75	0	0	1.04	0.8
33	27	41.8	56.9	0	0	0.83	1.13
33	26	85.7	64.1	0	0	1.85	1.29
37	32	79.5	85	0	0	1.09	1.13
26	29	54	57	0	0	0.76	0.82
28	29	71.3	73.7	11	6	1.17	1.22
33	**29**	**71.1**	**68.6**	**2**	**1**	**1.12**	**1.07**
5	**2**	**19.8**	**11.2**	**4**	**2**	**0.39**	**0.21**
31	33	84.7	77.3	7	10	0.87	0.82
29	28	98.3	123.2	13	12	1.27	1.57
26	38	85.7	96.9	3	0	1.21	1.37
24	32	92.8	106	0	0	1.22	1.4
37	28	142.1	90.1	2	5	1.93	1.24
25	24	81.8	82.2	0	0	1.25	1.28
38	40	145	131.5	17	4	1.9	1.7
30	**32**	**104.3**	**101.0**	**6**	**4**	**1.38**	**1.34**
6	**6**	**27.4**	**20.4**	**7**	**5**	**0.39**	**0.28**
31	29	45.2	56.2	4	6	0.8	0.97
37	42	51.3	101	3	7	0.62	1.25
25	31	83.5	71.5	0	0	1.56	1.34
31	37	71.4	46.8	3	0	0.83	0.55
29	27	57	76.8	10	9	1.12	1.54
22	26	87	77.5	0	0	1.23	1.1
33	27	117.6	102	6	3	1.84	1.55
30	**31**	**73.3**	**76.0**	**4**	**4**	**1.14**	**1.19**
5	**6**	**25.2**	**20.7**	**3**	**4**	**0.44**	**0.35**

Total Body Mass

Subject	Group	Gender	TBM (kg) Pre	TBM (kg) Post
1	Creatine	male	68.7	71.4
4	Creatine	male	97.3	98.0
11	Creatine	male	72.1	71.7
16	Creatine	male	70.2	72.2
17	Creatine	male	103.6	104.5
26	Creatine	male	97.3	96.8
32	Creatine	male	87.6	89.9
30	Creatine	male	76.3	79.3
	avg		**84.1**	**85.5**
	stdev		**14.0**	**13.5**
12	Creatine	female	90.3	93.7
19	Creatine	female	50.5	50.2
21	Creatine	female	46.2	49.5
22	Creatine	female	73.0	75.2
25	Creatine	female	71.0	69.5
27	Creatine	female	61.1	60.6
	avg		**65.4**	**66.5**
	stdev		**16.2**	**16.8**
2	Placebo	male	96.9	93.9
7	Placebo	male	77.3	78.6
10	Placebo	male	70.7	70.7
14	Placebo	male	76.0	75.7
15	Placebo	male	73.8	72.8
20	Placebo	male	65.4	64.4
23	Placebo	male	76.2	77.2
	avg		**76.6**	**76.2**
	stdev		**9.8**	**9.1**
3	2	female	56.3	57.7
9	2	female	82.7	81.0
13	2	female	53.5	53.4
18	2	female	85.9	85.8
31	2	female	50.9	50.0
29	2	female	70.6	70.2
24	2	female	63.8	65.6
	avg		66.2	66.2
	stdev		14.0	13.7

Body Composition - DEXA

Subject	Group	Gender	Body Fat (%)		LBM (g)		FM (g)	
			Pre	Post	Pre	Post	Pre	Post
16	Creatine	male	23.3	22.6	47494.5	50152.5	15141.5	15357.9
17	Creatine	male	26.0	24.0	66742.2	69714.6	24604.3	22999.4
26	Creatine	male	31.7	33.1	58107.2	57349.2	28270.7	29748.5
32	Creatine	male	30.1	30.5	53856.0	55656.4	24331.0	25587.3
30	Creatine	male	23.7	23.9	53597.4	54366.2	17548.5	17945.6
	avg		**27.0**	**26.8**	**55959.5**	**57447.8**	**21979.2**	**22327.7**
	stdev		**3.8**	**4.7**	**7115.8**	**7355.5**	**5440.4**	**5786.3**
19	Creatine	female	37.3	35.2	28247.2	29561.8	17922.9	1621.1
21	Creatine	female	16.8	18.1	34734.2	36466.2	7414.6	8491.1
22	Creatine	female	49.0	45.1	33602.8	37271.8	33826.7	31942.0
25	Creatine	female	38.8	35.4	38547.5	40702.2	25476.0	23243.3
27	Creatine	female	39.0	37.0	33466.9	34585.1	22465.4	21347.1
	avg		**36.2**	**34.2**	**33719.7**	**35717.4**	**21421.1**	**17328.9**
	stdev		**11.8**	**9.9**	**3686.6**	**4092.6**	**9744.9**	**12139.9**
20	Placebo	male	16.8	16.7	48209.7	47901.2	10177.0	10032.2
23	Placebo	male	19.8	19.5	55747.1	56150.6	14317.7	14226.5
	avg		**18.3**	**18.1**	**51978.4**	**52025.9**	**12247.4**	**12129.4**
	stdev		**2.1**	**2.0**	**5329.7**	**5833.2**	**2927.9**	**2965.8**
18	Placebo	female	46.7	45.8	39835.7	40728.3	37019.7	36478.3
31	Placebo	female	20.9	17.3	36221.9	37364.6	10130.6	8284.2
29	Placebo	female	41.7	41.6	36447.9	36776.8	27919.4	27925.9
24	Placebo	female	36.4	37.4	36350.5	36491.6	21849.6	22896.5
	avg		**36.4**	**35.5**	**37214.0**	**37840.3**	**24229.8**	**23896.2**
	stdev		**11.2**	**12.6**	**1750.2**	**1959.3**	**11279.0**	**11822.0**

Muscle Metabolites (mmol/kg dm)

Subject	Group	Gender	Pre				Post			
			ATP	PCr	Cr	TCr	ATP	PCr	Cr	TCr
1	Creatine	Male	15.97	61.52	71.04	132.57	18.82	103.74	59.81	163.55
4	Creatine	Male	18.00	78.16	28.65	106.81	11.62	57.37	78.39	135.76
16	Creatine	Male	19.05	55.62	57.37	112.99	16.06	77.78	54.99	132.77
17	Creatine	Male	21.74	84.49	38.47	122.97	28.10	112.00	81.90	193.90
26	Creatine	Male	18.43	84.77	33.06	117.83	25.75	108.49	74.44	182.93
30	Creatine	Male	17.03	30.52	61.50	92.03	15.34	73.62	66.92	140.53
32	Creatine	Male	16.79	76.55	56.00	132.55	23.94	83.05	82.42	165.47
	avg		**18.1**	**67.4**	**49.4**	**116.8**	**19.9**	**88.0**	**71.3**	**159.3**
	stdev		**1.9**	**19.7**	**16.0**	**14.5**	**6.1**	**20.5**	**10.9**	**23.9**
12	Creatine	Female	11.68	70.68	40.31	110.99	13.07	78.96	95.36	174.32
19	Creatine	Female	17.88	86.54	37.83	124.37	24.51	127.56	32.42	159.97
21	Creatine	Female	16.76	71.05	56.18	127.23	21.70	115.34	39.66	155.01
22	Creatine	Female	20.46	111.64	66.73	178.37	18.39	63.89	70.49	134.39
25	Creatine	Female	14.52	79.16	28.56	107.73	19.61	108.25	53.89	162.14
27	Creatine	Female	20.40	79.47	50.12	129.59	17.91	52.62	71.60	124.22
	avg		**17.0**	**83.1**	**46.6**	**129.7**	**19.2**	**91.1**	**60.6**	**151.7**
	stdev		**3.4**	**15.2**	**13.8**	**25.4**	**3.9**	**30.3**	**23.3**	**18.7**
2	Placebo	Male	22.36	101.41	41.50	142.91	16.01	63.82	38.66	102.48
7	Placebo	Male	22.78	112.33	15.81	128.13	23.90	85.50	70.70	156.20
10	Placebo	Male	22.10	91.90	76.80	168.70	20.86	73.30	77.47	150.77
14	Placebo	Male	19.43	90.82	33.24	124.07	14.86	65.91	23.33	89.24
15	Placebo	Male	12.24	38.75	73.80	112.55	12.41	35.93	78.84	114.77
20	Placebo	Male	21.89	76.51	69.12	145.63	18.95	72.96	48.29	121.25
23	Placebo	Male	21.58	112.44	50.83	163.27	19.68	97.55	45.90	143.46
	avg		**20.3**	**89.2**	**51.6**	**140.8**	**18.1**	**70.7**	**54.7**	**125.5**
	stdev		**3.7**	**25.6**	**22.9**	**20.6**	**3.9**	**19.3**	**21.3**	**25.4**
9	Placebo	Female	18.89	68.66	87.19	155.85	20.42	90.84	69.12	159.96
13	Placebo	Female	15.07	77.02	62.97	139.99	18.37	69.48	107.29	176.76
18	Placebo	Female	17.84	82.76	50.95	133.71	23.16	87.28	46.82	134.10
24	Placebo	Female	17.60	55.73	58.47	114.21	20.29	105.03	37.55	142.58
29	Placebo	Female	23.44	95.93	45.08	141.01	18.35	73.38	45.63	119.01
31	Placebo	Female	20.82	68.97	77.19	146.16	24.82	85.03	67.83	152.86
	avg		**18.9**	**74.8**	**63.6**	**138.5**	**20.9**	**85.2**	**62.4**	**147.5**
	stdev		**2.9**	**13.8**	**15.9**	**14.0**	**2.6**	**12.8**	**25.4**	**20.3**

Isometric Data

Subject	Group	Gender	Handgrip (kg) Pre	Handgrip (kg) Post	Dorsiflexion (Nm) Pre	Dorsiflexion (Nm) Post	Knee Extension (Nm) Pre	Knee Extension (Nm) Post
1	Creatine	male	495.7	634.6	66.5	84.7	154	212.4
4	Creatine	male	447	519.4	57.5	71.3	136.4	283.1
11	Creatine	male	416.7	421.9	68	75.2	182.5	172.4
16	Creatine	male	315.3	327.8	39.1	47.6		
17	Creatine	male	526.6	535.8	64	66.7	196.4	233.2
26	Creatine	male	430.5	507.5	58.7	64	152.2	190.9
32	Creatine	male	412.7	410.1	46.4	50	114.9	200
30	Creatine	male	462.1	396.3	29.2	40.1	135.2	224.8
	avg		**438.33**	**469.18**	**53.68**	**62.45**	**153.09**	**216.69**
	stdev		**63.30**	**97.70**	**14.04**	**15.27**	**28.28**	**35.76**
12	Creatine	female	375.9	376.5	38.2	42.7	136.6	161.1
19	Creatine	female	227.8	231.7	31.9	34.3	36.5	80
21	Creatine	female	229.7	170.5	38.1	45.3	85.7	129
22	Creatine	female	290.9	318.6	42.4	38.9	132.9	145.4
25	Creatine	female	246.2	246.8	40.9	41.4	96.1	126.2
27	Creatine	female	182.3	208	32.7	30.7	75.8	112.4
	avg		**258.80**	**258.68**	**37.37**	**38.88**	**93.93**	**125.68**
	stdev		**67.17**	**75.74**	**4.26**	**5.48**	**37.52**	**27.99**
2	Placebo	male	355.5	421.3	40.9	52.2	135.7	158.4
7	Placebo	male	355.5	353.5	51.1	33.1	185.6	191.7
10	Placebo	male	429.2	452.2	58.3	59.5	177.2	201.4
14	Placebo	male	354.8	402.9	61.3	61.2	151	192
15	Placebo	male	506.9	474.6	57.4	56.4	177.9	189.7
20	Placebo	male	380.5	348.2	44.5	43.8	94.6	122
23	Placebo	male	398.9	389.7	52.3	57.8	166.7	202.9
	avg		**397.33**	**406.06**	**52.26**	**52.00**	**155.53**	**179.73**
	stdev		**55.70**	**47.34**	**7.47**	**10.15**	**31.95**	**29.40**
3	Placebo	female	244.9	262	35.4	45.1	95.1	128.2
9	Placebo	female	239.6	245.5	36.6	35.6	74.9	83.7
13	Placebo	female	251.5	242.9	19.5	32.5	63	87
18	Placebo	female	243.6	237	26.1	24	87.4	95.8
31	Placebo	female	287	292.3	46.3	55.3	102.6	148.8
29	Placebo	female	260.7	268.6	32	39.3	112.9	125.4
24	Placebo	female	323.9	317.3	42.9	41.9	85.2	124.8
	avg		**264.46**	**266.51**	**34.11**	**39.10**	**88.73**	**113.39**
	stdev		**30.71**	**29.27**	**9.27**	**9.92**	**16.76**	**24.61**

1 RM - Knee Extension

Subject	Group	Gender	Knee Extension			
			Pre	Post	Increase	%Increase
1	Creatine	male	120	160	40	33.3
4	Creatine	male	130	210	80	61.5
11	Creatine	male	100	152	52	52.0
17	Creatine	male	110	145	35	31.8
26	Creatine	male	145	170	25	17.2
32	Creatine	male	95	134	39	41.1
30	Creatine	male	130	164	34	26.2
	avg		**118.6**	**162.1**	**43.6**	**37.6**
	stdev		**18.0**	**24.3**	**18.0**	**15.2**
2	Placebo	male	110	165	55	50.0
7	Placebo	male	140	165	25	17.9
10	Placebo	male	90	140	50	55.6
14	Placebo	male	110	140	30	27.3
15	Placebo	male	90	115	25	27.8
20	Placebo	male	60	122	62	103.3
23	Placebo	male	150	210	60	40.0
	avg		**107.1**	**151.0**	**43.9**	**46.0**
	stdev		**30.9**	**32.3**	**16.6**	**28.6**
12	Creatine	female	90	150	60	66.7
19	Creatine	female	63	90	27	42.9
21	Creatine	female	65	100	35	53.8
22	Creatine	female	65	124	59	90.8
25	Creatine	female	70	100	30	42.9
27	Creatine	female	77	114	37	48.1
	avg		**71.7**	**113.0**	**41.3**	**57.5**
	stdev		**10.3**	**21.7**	**14.5**	**18.6**
3	Placebo	female	50	125	75	150.0
9	Placebo	female	70	105	35	50.0
13	Placebo	female	65	92	27	41.5
18	Placebo	female	95	123	28	29.5
31	Placebo	female	77	135	58	75.3
29	Placebo	female	60	100	40	66.7
24	Placebo	female	100	125	25	25.0
	avg		**73.9**	**115.0**	**41.1**	**62.6**
	stdev		**18.2**	**15.9**	**18.7**	**42.7**

1 RM - Leg Press

Subject	Group	Gender	Leg Press Pre	Post	Increase	%Increase
4	Creatine	male	270	340	70	25.9
11	Creatine	male	190	248	58	30.5
17	Creatine	male	210	234	24	11.4
26	Creatine	male	185	234	49	26.5
32	Creatine	male	127	169	42	33.1
30	Creatine	male	180	240	60	33.3
	avg		**193.7**	**244.2**	**50.5**	**26.8**
	stdev		**46.5**	**54.9**	**16.1**	**8.2**
2	Placebo	male	160	285	125	78.1
7	Placebo	male	185	205	20	10.8
10	Placebo	male	215	255	40	18.6
14	Placebo	male	140	215	75	53.6
15	Placebo	male	200	245	45	22.5
20	Placebo	male	100	189	89	89.0
23	Placebo	male	160	220	60	37.5
	avg		**165.7**	**230.6**	**64.9**	**44.3**
	stdev		**38.8**	**32.9**	**35.0**	**30.4**
12	Creatine	female	160	252	92	57.5
19	Creatine	female	80	100	20	25.0
21	Creatine	female	105	145	40	38.1
22	Creatine	female	105	149	44	41.9
25	Creatine	female	90	110	20	22.2
27	Creatine	female	124	164	40	32.3
	avg		**110.7**	**153.3**	**42.7**	**36.2**
	stdev		**28.4**	**54.1**	**26.4**	**12.9**
3	Placebo	female	90	140	50	55.6
9	Placebo	female	110	190	80	72.7
13	Placebo	female	70	134	64	91.4
18	Placebo	female	110	150	40	36.4
31	Placebo	female	84	104	20	23.8
29	Placebo	female	145	185	40	27.6
24	Placebo	female	124	160	36	29.0
	avg		**104.7**	**151.9**	**47.1**	**48.1**
	stdev		**25.5**	**29.9**	**19.7**	**26.0**

1 RM - Seated Chest Press

Subject	Group	Gender	Seated Chest Press Pre	Post	Increase	%Increase
1	Creatine	male	145	167	22	15.2
4	Creatine	male	150	210	60	40.0
11	Creatine	male	95	140	45	47.4
16	Creatine	male	110	134	24	21.8
17	Creatine	male	120	135	15	12.5
32	Creatine	male	77	110	33	42.9
30	Creatine	male	113	125	12	10.6
	avg		**115.7**	**145.9**	**30.1**	**27.2**
	stdev		**25.9**	**33.1**	**17.2**	**15.7**
2	Placebo	male	90	120	30	33.3
7	Placebo	male	80	105	25	31.3
10	Placebo	male	120	135	15	12.5
14	Placebo	male	120	135	15	12.5
15	Placebo	male	110	130	20	18.2
20	Placebo	male	68	97	29	42.6
23	Placebo	male	93	113	20	21.5
	avg		**97.3**	**119.3**	**22.0**	**24.6**
	stdev		**20.1**	**15.0**	**6.2**	**11.5**
12	Creatine	female	70	105	35	50.0
19	Creatine	female	40	47	7	17.5
21	Creatine	female	45	55	10	22.2
22	Creatine	female	47	60	13	27.7
25	Creatine	female	44	55	11	25.0
27	Creatine	female	43	54	11	25.6
	avg		**48.2**	**62.7**	**14.5**	**28.0**
	stdev		**10.9**	**21.2**	**10.2**	**11.3**
3	Placebo	female	35	54	19	54.3
9	Placebo	female	45	60	15	33.3
13	Placebo	female	35	45	10	28.6
18	Placebo	female	48	53	5	10.4
29	Placebo	female	55	73	18	32.7
24	Placebo	female	56	70	14	25.0
	avg		**45.7**	**59.2**	**13.5**	**30.7**
	stdev		**9.2**	**10.7**	**5.2**	**14.3**

1 RM - Arm Flexion

Subject	Group	Gender	Arm Flexion			
			Pre	Post	Increase	%Increase
1	Creatine	male	110	127	17	15.5
4	Creatine	male	110	140	30	27.3
11	Creatine	male	70	95	25	35.7
16	Creatine	male	70	102	32	45.7
17	Creatine	male	80	120	40	50.0
26	Creatine	male	45	87	42	93.3
32	Creatine	male	70	104	34	48.6
30	Creatine	male	92	124	32	34.8
	avg		**80.9**	**112.4**	**31.5**	**43.9**
	stdev		**22.2**	**18.1**	**8.0**	**23.1**
2	Placebo	male	50	75	25	50.0
7	Placebo	male	45	75	30	66.7
10	Placebo	male	85	117	32	37.6
14	Placebo	male	60	90	30	50.0
15	Placebo	male	80	90	10	12.5
20	Placebo	male	50	70	20	40.0
23	Placebo	male	52	75	23	44.2
	avg		**60.3**	**84.6**	**24.3**	**43.0**
	stdev		**15.9**	**16.3**	**7.6**	**16.5**
12	Creatine	female	32	55	23	71.9
19	Creatine	female	18	23	5	27.8
21	Creatine	female	35	45	10	28.6
22	Creatine	female	22	38	16	72.7
25	Creatine	female	20	35	15	75.0
27	Creatine	female	22	44	22	100.0
	avg		**24.8**	**40.0**	**15.2**	**62.7**
	stdev		**6.9**	**10.8**	**6.9**	**28.7**
3	Placebo	female	27	40	13	48.1
9	Placebo	female	30	41	11	36.7
13	Placebo	female	15	30	15	100.0
18	Placebo	female	30	40	10	33.3
31	Placebo	female	22	42	20	90.9
29	Placebo	female	20	35	15	75.0
24	Placebo	female	40	50	10	25.0
	avg		**26.3**	**39.7**	**13.4**	**58.4**
	stdev		**8.2**	**6.2**	**3.6**	**30.0**

Functional Data

Subject	Group	Gender	Timed Walk Test (s)		Timed Walk Test (m/s)		Timed Stair Test (s)	
			Pre	Post	Pre	Post	Pre	Post
1	Creatine	male	15.76	17.07	1.90	1.76	6.58	5.78
4	Creatine	male	16.77	15.9	1.79	1.89	4.36	4.22
11	Creatine	male	19.78	14.6	1.52	2.05	8.43	6.28
16	Creatine	male	18.94	15.82	1.58	1.90	8.47	8.40
17	Creatine	male	13.78	13.69	2.18	2.19	6.38	7.66
26	Creatine	male	15.03	12.13	2.00	2.47	5.41	4.52
32	Creatine	male	17.5	16.1	1.71	1.86	6.81	5.41
30	Creatine	male	16.47	14.68	1.82	2.04	5.78	5.00
	avg		**16.75**	**15.00**	**1.81**	**2.02**	**6.53**	**5.91**
	stdev		**1.98**	**1.57**	**0.22**	**0.23**	**1.41**	**1.48**
12	Creatine	female	17.09	15.41	1.76	1.95	6.59	5.81
19	Creatine	female	20.53	19.31	1.46	1.55	6.5	5.75
21	Creatine	female	17.55	14.72	1.71	2.04	8.12	4.61
22	Creatine	female	17.81	15.47	1.68	1.94	7.41	5.21
25	Creatine	female	21.41	19.66	1.40	1.53	8.62	8.44
27	Creatine	female	17.69	17.22	1.70	1.74	6.82	5.48
	avg		**18.68**	**16.97**	**1.62**	**1.79**	**7.34**	**5.88**
	stdev		**1.81**	**2.12**	**0.15**	**0.22**	**0.87**	**1.33**
2	Placebo	male	20.21	13.5	1.48	2.22	9.79	5.78
7	Placebo	male	10.32	11.91	2.91	2.52	6.22	6
10	Placebo	male	16.38	16.52	1.83	1.82	6.19	6.41
14	Placebo	male	13.69	11.91	2.19	2.52	6.32	4.87
15	Placebo	male	14.16	13.63	2.12	2.20	6.59	4.69
20	Placebo	male	19.69	16.43	1.52	1.83	9.63	5.98
23	Placebo	male	14.88	14.73	2.02	2.04	5.25	4.36
	avg		**15.62**	**14.09**	**2.01**	**2.16**	**7.14**	**5.44**
	stdev		**3.48**	**1.91**	**0.48**	**0.29**	**1.80**	**0.79**
3	Placebo	female	18.8	16.1	1.60	1.86	7.3	4.84
9	Placebo	female	20.35	18.53	1.47	1.62	9.63	6.47
13	Placebo	female	19.44	20.53	1.54	1.46	8.69	7.56
18	Placebo	female	21.62	18.28	1.39	1.64	8.09	7.65
31	Placebo	female	13.34	12.46	2.25	2.41	5.07	4.9
29	Placebo	female	16.75	14.79	1.79	2.03	5.88	4.42
24	Placebo	female	16.25	14.23	1.85	2.11	5.34	4.81
	avg		**18.08**	**16.42**	**1.70**	**1.88**	**7.14**	**5.81**
	stdev		**2.82**	**2.83**	**0.29**	**0.33**	**1.76**	**1.39**

Timed Chair Rise (number of complete rises in 30 sec)

Subject	GROUP	GENDER	Pre	Post
11	Creatine	male	13	18
16	Creatine	male	15	17
17	Creatine	male	14	14
26	Creatine	male	15	17
32	Creatine	male	13	16
	avg		**14.0**	**16.4**
	stdev		**1.0**	**1.5**
12	Creatine	female	15	19
19	Creatine	female	11	14
21	Creatine	female	10	14
22	Creatine	female	13	18
25	Creatine	female	12	14
27	Creatine	female	21	31
	avg		**13.7**	**18.3**
	stdev		**4.0**	**6.6**
14	Placebo	male	18	20
15	Placebo	male	14	13
20	Placebo	male	11	10
23	Placebo	male	18	23
	avg		**15.3**	**16.5**
	stdev		**3.4**	**6.0**
13	Placebo	female	9	15
18	Placebo	female	0	0
31	Placebo	female	16	28
29	Placebo	female	21	26
24	Placebo	female	16	16
	avg		**12.4**	**17.0**
	stdev		**8.1**	**11.1**

Fiber Area (um^2)

			Type I		Type IIa		Type IIx	
Subject	Group	Gender	Pre	Post	Pre	Post	Pre	Post
1	Creatine	male	4619	5253	3886	5553	2497	3854
4	Creatine	male	3640	4756	3512	4353	3132	4279
11	Creatine	male	5773	4735	4763	5219	2047	3569
16	Creatine	male	6286	5088	5041	3458	4814	3199
17	Creatine	male	3740	4861	5914	5787	4630	4753
26	Creatine	male	3670	3301	6237	6242	5525	7332
30	Creatine	male	7032	8690	6179	7471	3790	4849
32	Creatine	male	4088	7131	4904	10760	4768	8151
	avg		**4856**	**5477**	**5055**	**6105**	**3900**	**4998**
	stdev		**1331**	**1667**	**1018**	**2230**	**1240**	**1796**
12	Creatine	female	2669	1548	3030	2037	1571	1505
19	Creatine	female	3644	3696	2033	1635	1365	1120
21	Creatine	female	3738	5331	2521	3791	1466	4410
22	Creatine	female	4743	4558	3933	4336	2858	2655
25	Creatine	female	3653	4351	2976	3307	1614	3299
27	Creatine	female	5039	5149	4892	3121	1979	2265
	avg		**3914**	**4106**	**3231**	**3038**	**1809**	**2542**
	stdev		**857**	**1383**	**1029**	**1030**	**555**	**1204**
2	Placebo	male	4230	5053	4821	7706	3122	4174
7	Placebo	male	4030	5109	4155	3522	3416	2834
10	Placebo	male	3916	3791	3178	4545	2286	3863
14	Placebo	male	5138	6062	3631	4388	2729	2539
15	Placebo	male	3895	5920	4605	7178	2474	7377
20	Placebo	male	6834	6682	4451	3395	3267	3312
23	Placebo	male	4790	8173	4740	6139	3002	4433
	avg		**4690**	**5827**	**4226**	**5268**	**2899**	**4076**
	stdev		**1056**	**1388**	**615**	**1742**	**418**	**1611**
3	Placebo	female	3398	4082	2244	2667	1495	1643
9	Placebo	female	5930	5149	3747	4005	3420	3190
13	Placebo	female	4699	7295	3878	4232	2577	2779
18	Placebo	female	3012	4374	2402	4062	1611	4100
24	Placebo	female	4672	4862	3232	2508	2532	2213
29	Placebo	female	4646	3348	2950	2765	1658	2104
31	Placebo	female	3927	2795	3516	2420	2454	2405
	avg		**4326**	**4558**	**3138**	**3237**	**2250**	**2633**
	stdev		**973**	**1459**	**639**	**817**	**698**	**814**

Fiber Area (%)

Subject	Group	Gender	Type I		Type IIa		Type IIx	
			Pre	Post	Pre	Post	Pre	Post
1	Creatine	Male	69.5	45.1	26.8	36.6	3.7	18.3
4	Creatine	Male	35.7	38.6	48	28.7	16.3	32.7
11	Creatine	Male	37.8	28.6	54.7	39.6	7.5	31.7
16	Creatine	Male	54	53.9	33.9	29.3	12.1	16.9
17	Creatine	Male	33.7	50.7	38.7	34.4	27.6	14.9
26	Creatine	Male	21.6	8.5	17.8	32.1	60.6	59.3
30	Creatine	Male	40.2	57.4	53.3	38.4	6.5	4.2
32	Creatine	Male	31.3	29.2	38.7	39.4	30	31.5
	avg		**40.5**	**39.0**	**39.0**	**34.8**	**20.5**	**26.2**
	stdev		**14.8**	**16.3**	**12.9**	**4.4**	**18.8**	**16.7**
12	Creatine	Female	63.3	53.2	30.5	31.6	6.2	15.2
19	Creatine	Female	72.8	72.5	23.3	20.2	3.9	15.5
21	Creatine	Female	84.7	68.1	14.6	28.4	0.7	3.5
22	Creatine	Female	37.3	42.7	34.4	42	28.3	15.3
25	Creatine	Female	54.9	50.4	31.7	45.3	13.4	4.3
27	Creatine	Female	36.5	44.3	48.2	53.1	15.3	2.6
	avg		**58.3**	**55.2**	**30.5**	**36.8**	**11.3**	**9.4**
	stdev		**19.3**	**12.4**	**11.3**	**12.2**	**10.0**	**6.5**
2	Placebo	Male	41.1	32.6	46.2	26.7	12.7	40.7
7	Placebo	Male	47.2	41.9	30.9	34.6	22	23.5
10	Placebo	Male	41.4	37.5	53.7	38.8	4.9	23.7
14	Placebo	Male	44.7	61.9	36.7	25.3	18.6	12.8
15	Placebo	Male	45.4	36.7	42.7	27.8	11.9	35.5
20	Placebo	Male	45.1	64.3	40.3	30.4	14.6	5.3
23	Placebo	Male	26.6	50.5	33.2	28	40.1	21.5
	avg		**41.6**	**46.5**	**40.5**	**30.2**	**17.8**	**23.3**
	stdev		**7.0**	**12.7**	**7.9**	**4.8**	**11.2**	**12.2**
3	Placebo	Female	64	60.4	21.2	29.8	14.7	9.8
9	Placebo	Female	52.3	35.2	25.7	34.6	22	29.9
13	Placebo	Female	22.5	55.1	39.2	33.9	38.4	11
18	Placebo	Female	74.3	62.9	15.1	23.1	10.6	14
24	Placebo	Female	60.4	82	29	7.1	10.6	10.9
29	Placebo	Female	33.8	32	59	30.9	7.3	37.1
31	Placebo	Female	69.2	65.5	24.8	32.2	6	2.3
	avg		**53.8**	**56.2**	**30.6**	**27.4**	**15.7**	**16.4**
	stdev		**19.1**	**17.5**	**14.5**	**9.7**	**11.3**	**12.4**

Fiber distribution (%)

			Type I		Type IIa		Type IIx	
Subject	Group	Gender	Pre	Post	Pre	Post	Pre	Post
1	Creatine	Male	65.2	44	28.8	33	6	23
4	Creatine	Male	35	38.6	47.3	28	17.7	33.5
11	Creatine	Male	31.1	26.5	53.3	35.1	15.6	38.5
16	Creatine	Male	50.3	45	35.3	33.5	14.4	21.5
17	Creatine	Male	41.2	53.4	31	30.3	27.7	16.3
26	Creatine	Male	30.3	15.1	14.5	30.6	55.2	54.3
30	Creatine	Male	37.5	55.9	51.8	37.3	10.7	6.8
32	Creatine	Male	34.5	34	36.7	32.5	28.8	33.5
	avg		**40.6**	**39.1**	**37.3**	**32.5**	**22.0**	**28.4**
	stdev		**11.8**	**13.7**	**13.1**	**2.9**	**15.5**	**14.7**
12	Creatine	Female	63.5	58	26.5	25.4	10	16.6
19	Creatine	Female	60.4	53.3	31.4	30.8	8.2	15.9
21	Creatine	Female	79.3	61.1	19	35.5	1.6	3.4
22	Creatine	Female	29.9	38.2	32.8	40	37.3	21.8
25	Creatine	Female	45.8	44.2	30.9	51	23.3	4.7
27	Creatine	Female	29.9	33.4	39.5	62.2	30.5	4.4
	avg		**51.5**	**48.0**	**30.0**	**40.8**	**18.5**	**11.1**
	stdev		**19.8**	**11.2**	**6.8**	**13.6**	**14.0**	**7.9**
2	Placebo	Male	41.3	33	42.6	19.2	16.1	47.8
7	Placebo	Male	45.3	31.8	29.3	37.6	25.4	30.6
10	Placebo	Male	36.4	39.2	56.5	35.1	7.1	25.7
14	Placebo	Male	35.4	51.3	38.9	24.9	25.7	23.8
15	Placebo	Male	46.2	42.8	35.9	27.1	17.9	30.1
20	Placebo	Male	32.5	51.6	45.9	40.1	21.6	8.3
23	Placebo	Male	22.4	40.3	27.6	29	50	30.7
	avg		**37.1**	**41.4**	**39.5**	**30.4**	**23.4**	**28.1**
	stdev		**8.2**	**7.9**	**10.0**	**7.5**	**13.3**	**11.7**
3	Placebo	Female	50.3	47.1	25.3	35	24.4	17.9
9	Placebo	Female	42.1	29.1	29.4	34.2	28.5	36.7
13	Placebo	Female	17.3	41.2	33.6	39.6	49.1	19.2
18	Placebo	Female	66.7	59.9	16.3	25	17	15.1
24	Placebo	Female	50.7	70.8	33.8	10.5	15.5	18.7
29	Placebo	Female	24	26	63.6	29.2	12.4	44.9
31	Placebo	Female	67.1	63.3	24.6	34.3	8.3	2.4
	avg		**45.5**	**48.2**	**32.4**	**29.7**	**22.2**	**22.1**
	stdev		**19.3**	**17.2**	**15.0**	**9.6**	**13.7**	**14.2**

Dehydroepiandrosterone (umol/L)

Subject	Group	Gender	Pre	Post
1	Creatine	male	0.9032	0.8255
4	Creatine	male	6.9956	1.2739
11	Creatine	male	4.8472	5.0018
16	Creatine	male	5.6119	5.9688
17	Creatine	male	2.1344	1.6677
26	Creatine	male	4.2593	4.0506
30	Creatine	male	2.4747	2.7362
32	Creatine	male	2.6575	2.6821
	avg		**3.74**	**3.03**
	stdev		**2.04**	**1.84**
12	Creatine	female	1.9322	1.909
19	Creatine	female	0.2732	0.3107
21	Creatine	female	1.6705	0.6535
22	Creatine	female	4.0607	1.6113
25	Creatine	female	3.3099	3.5217
27	Creatine	female	2.462	2.9835
	avg		**2.28**	**1.83**
	stdev		**1.33**	**1.26**
2	Placebo	male	0.3489	0.2739
7	Placebo	male	1.8986	1.5105
10	Placebo	male	3.4277	3.4114
14	Placebo	male	2.8119	2.0964
15	Placebo	male	3.534	3.772
20	Placebo	male	5.3173	4.8057
23	Placebo	male	2.3318	3.5049
	avg		**2.81**	**2.77**
	stdev		**1.54**	**1.55**
3	Placebo	female	0.4817	0.6041
9	Placebo	female	0.6968	0.5797
13	Placebo	female	1.3176	1.6897
18	Placebo	female	1.6071	2.06416
24	Placebo	female	2.8627	2.0999
29	Placebo	female	1.4135	1.2382
31	Placebo	female	3.4359	3.4141
	avg		**1.69**	**1.67**
	stdev		**1.09**	**0.99**

Total Testosterone (nmol/L)

Subject	Group	Gender	Pre	Post
1	Creatine	male	9.74	12.97
4	Creatine	male	9.75	12.26
11	Creatine	male	11.58	16.26
16	Creatine	male	26.16	24.86
17	Creatine	male	12.77	23.61
26	Creatine	male	15.21	12.63
30	Creatine	male	20.27	14.33
32	Creatine	male	17.61	15.99
	avg		**15.38**	**16.61**
	stdev		**5.36**	**4.94**
12	Creatine	female	0.57	0.69
19	Creatine	female	0.07	0.20
21	Creatine	female	0.35	0.15
22	Creatine	female	1.13	1.11
25	Creatine	female	1.04	0.92
27	Creatine	female	0.79	0.61
	avg		**0.66**	**0.61**
	stdev		**0.37**	**0.38**
2	Placebo	male	14.48	20.44
7	Placebo	male	9.67	23.48
10	Placebo	male	22.83	30.65
14	Placebo	male	46.06	31.41
15	Placebo	male	11.84	16.57
20	Placebo	male	12.19	15.48
23	Placebo	male	17.96	20.28
	avg		**19.29**	**22.62**
	stdev		**12.60**	**6.33**
3	Placebo	female	0.14	0.24
13	Placebo	female	0.45	0.72
18	Placebo	female	0.53	1.04
24	Placebo	female	0.19	0.25
29	Placebo	female	0.47	0.34
31	Placebo	female	0.21	0.04
	avg		**0.33**	**0.44**
	stdev		**0.17**	**0.37**

Insulin-like Growth Factor-1 (nmol/L)

Subject	Group	Gender	Pre	Post
1	Creatine	male	8.83	7.92
4	Creatine	male	8.92	9.42
11	Creatine	male	15.84	16.34
17	Creatine	male	9.83	11.42
26	Creatine	male	8.92	9.42
	avg		**10.47**	**10.90**
	stdev		**3.03**	**3.29**
12	Creatine	female	9.25	8.00
21	Creatine	female	10.25	4.25
22	Creatine	female	6.25	6.25
25	Creatine	female	10.42	8.25
27	Creatine	female	14.75	14.76
	avg		**10.18**	**8.30**
	stdev		**3.05**	**3.95**
2	Placebo	male	7.00	6.75
10	Placebo	male	10.50	8.33
14	Placebo	male	6.00	8.67
20	Placebo	male	6.33	6.66
23	Placebo	male	15.42	9.67
	avg		**9.05**	**8.02**
	stdev		**3.99**	**1.29**
3	Placebo	female	3.49	5.91
13	Placebo	female	9.83	8.08
18	Placebo	female	9.50	8.50
24	Placebo	female	8.00	7.16
29	Placebo	female	5.58	5.66
	avg		**7.28**	**7.06**
	stdev		**2.70**	**1.26**

Osteocalcin (ng/mL)

Subject	Group	Gender	Pre	Post
1	Creatine	male	9.85	11.38
4	Creatine	male	13.90	14.72
11	Creatine	male	23.10	17.08
16	Creatine	male	11.49	13.42
17	Creatine	male	21.38	19.42
26	Creatine	male	15.64	18.02
30	Creatine	male	16.72	17.59
32	Creatine	male	15.57	16.88
	avg		**15.96**	**16.06**
	stdev		**4.52**	**2.67**
12	Creatine	female	13.07	13.50
19	Creatine	female	11.97	15.97
21	Creatine	female	17.17	17.89
22	Creatine	female	13.97	12.65
25	Creatine	female	24.80	25.34
27	Creatine	female	21.44	22.39
	avg		**17.07**	**17.96**
	stdev		**5.11**	**5.02**
2	Placebo	male	13.42	14.70
7	Placebo	male	15.49	12.79
10	Placebo	male	15.90	15.90
14	Placebo	male	12.14	15.69
15	Placebo	male	13.63	13.15
20	Placebo	male	16.89	15.43
23	Placebo	male	11.03	11.11
	avg		**14.07**	**14.11**
	stdev		**2.12**	**1.80**
3	Placebo	female	12.90	16.52
9	Placebo	female	19.31	19.16
13	Placebo	female	11.64	12.14
18	Placebo	female	16.89	17.54
24	Placebo	female	20.75	22.67
29	Placebo	female	13.49	14.39
31	Placebo	female	19.00	14.00
	avg		**16.28**	**16.63**
	stdev		**3.60**	**3.55**

Creatine Kinase Activity (U/L)

Subject	Group	Gender	Pre	Post
1	Creatine	male	99.95	192.76
4	Creatine	male	50.83	130.71
11	Creatine	male	41.07	59.61
16	Creatine	male	101.67	82.96
17	Creatine	male	45.92	36.68
26	Creatine	male	32.37	77.72
30	Creatine	male	12.87	244.64
32	Creatine	male	41.84	34.07
	avg		**53.315**	**107.3938**
	stdev		**31.46426**	**76.34996**
12	Creatine	female	26.89	25.98
19	Creatine	female	253.77	301.36
21	Creatine	female	33.62	53.34
22	Creatine	female	62.01	117.26
25	Creatine	female	67.67	100.36
27	Creatine	female	55.87	75.23
	avg		**83.305**	**112.255**
	stdev		**85.04137**	**98.19618**
2	Placebo	male	64.51	85.09
7	Placebo	male	49.89	22.13
10	Placebo	male	28.24	35.43
14	Placebo	male	106.35	110.24
15	Placebo	male	54.1	62.09
20	Placebo	male	135.01	122.78
23	Placebo	male	147.43	135.52
	avg		**83.64714**	**81.89714**
	stdev		**45.95392**	**43.74921**
3	Placebo	female	20.71	21.81
9	Placebo	female	111.99	57.59
13	Placebo	female	33.86	30.4
18	Placebo	female	62.03	53.46
24	Placebo	female	74.04	86.53
29	Placebo	female	40.54	29.5
31	Placebo	female	130.22	49.70857
	avg		**67.62714**	**46.9998**
	stdev		**40.89322**	**22.13663**

Plasma Creatinine (umol/L)

Subject	Group	Gender	Pre	Post
1	Creatine	male	100.2	111.5
4	Creatine	male	137.5	179.9
11	Creatine	male	132.8	162.9
16	Creatine	male	72.9	96.2
17	Creatine	male	102.4	90.2
26	Creatine	male	117.9	104.8
30	Creatine	male	139.2	150.0
32	Creatine	male	88.6	113.9
	avg		**111.4**	**126.2**
	stdev		**24.4**	**33.4**
12	Creatine	female	74.9	92.1
19	Creatine	female	85.1	119.1
21	Creatine	female	81.7	127.4
22	Creatine	female	108.4	130.3
25	Creatine	female	111.4	128.6
27	Creatine	female	110.8	100.2
	avg		**95.4**	**116.3**
	stdev		**16.6**	**16.3**
2	Placebo	male	62.4	63.1
7	Placebo	male	101.5	84.8
10	Placebo	male	94.9	94.5
14	Placebo	male	116.6	134.7
15	Placebo	male	148.9	100.1
20	Placebo	male	141.8	98.3
23	Placebo	male	89.7	94.5
	avg		**107.9**	**95.7**
	stdev		**30.3**	**21.3**
3	Placebo	female	125.1	113.5
9	Placebo	female	95.7	97.3
13	Placebo	female	105.5	86.9
18	Placebo	female	113.5	106.4
24	Placebo	female	69.8	63.4
29	Placebo	female	81.7	119.8
31	Placebo	female	112.3	37.8
	avg		**100.5**	**89.3**
	stdev		**19.4**	**29.4**

γ-glutamyl transfrase (U/L)

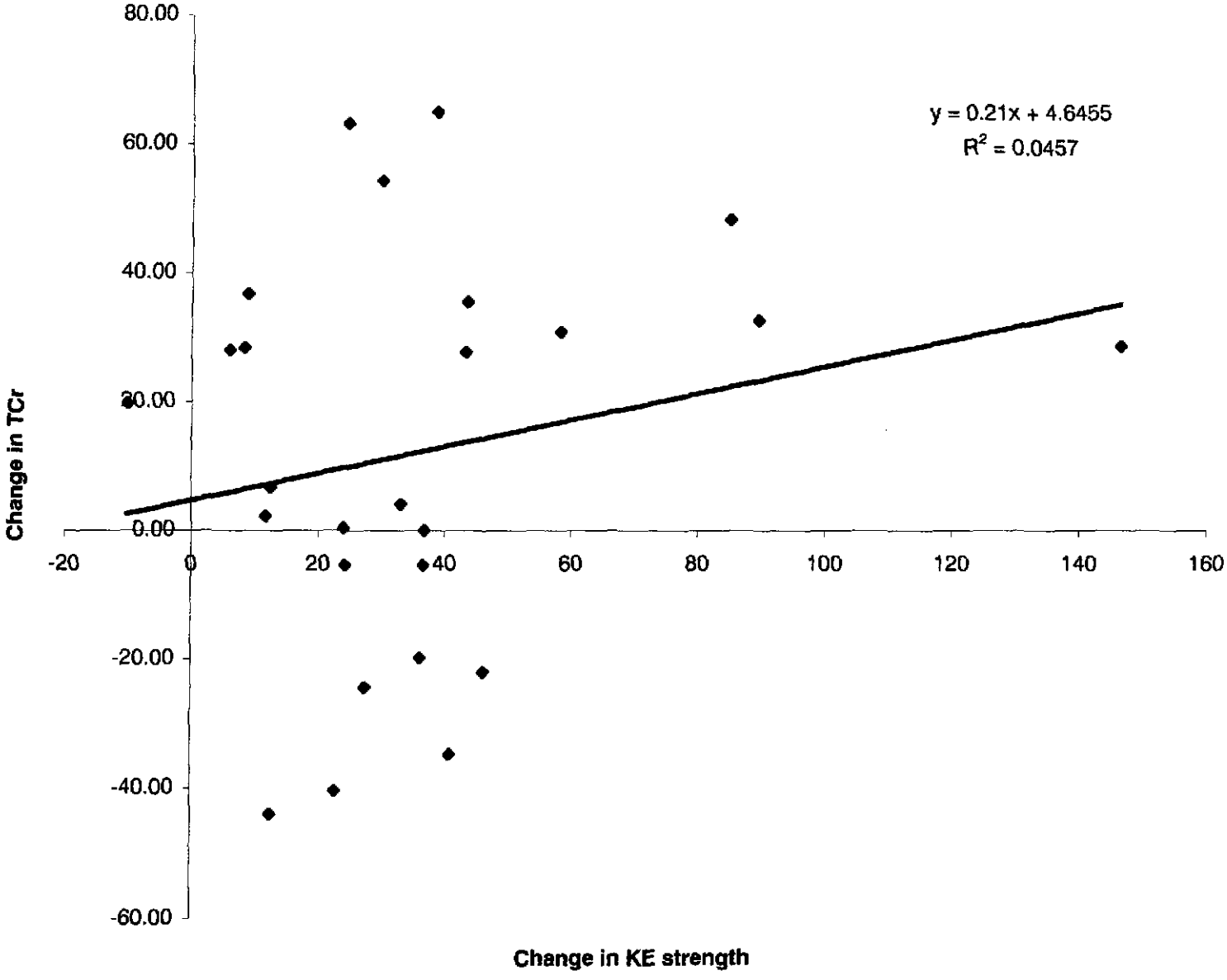
Subject	Group	Gender	Pre	Post
1	Creatine	male	16	15
4	Creatine	male	88	70
11	Creatine	male	29	28
16	Creatine	male	20	23
17	Creatine	male	24	20
26	Creatine	male	18	19
30	Creatine	male	23	20
32	Creatine	male	33	32
	avg		**31.4**	**28.4**
	stdev		**23.6**	**17.7**
12	Creatine	female	16	15
19	Creatine	female	14	14
21	Creatine	female	18	17
22	Creatine	female	21	23
25	Creatine	female	18	17
27	Creatine	female	19	21
	avg		**17.7**	**17.8**
	stdev		**2.4**	**3.5**
2	Placebo	male	25	34
10	Placebo	male	20	20
14	Placebo	male	39	23
15	Placebo	male	28	28
20	Placebo	male	14	14
23	Placebo	male	22	21
	avg		**24.7**	**23.3**
	stdev		**8.5**	**6.9**
3	Placebo	female	35	39
9	Placebo	female	19	16
13	Placebo	female	14	14
18	Placebo	female	21	21
24	Placebo	female	61	57
29	Placebo	female	19	20
31	Placebo	female	27	30
	avg		**28.0**	**28.1**
	stdev		**16.1**	**15.4**

Urine Creatinine and Creatine

Subject	Group	Gender	Creatinine (mg/mL) Pre	Creatinine (mg/mL) Post	Creatine (mg/mL) Pre	Creatine (mg/mL) Post
1	Creatine	male	0.78	0.90	2.07	2.04
4	Creatine	male	1.05	1.67	0.71	1.96
11	Creatine	male	1.53	1.19	1.02	5.66
16	Creatine	male	0.25	0.31	0.11	0.20
17	Creatine	male	0.90	1.37	0.82	4.55
26	Creatine	male	1.22	0.99	0.56	-0.03
30	Creatine	male	0.70	0.70	0.44	3.34
32	Creatine	male	0.98	1.23	0.65	0.14
	avg		**0.92**	**1.05**	**0.80**	**2.23**
	stdev		**0.378999**	**0.420917**	**0.580267**	**2.140507**
12	Creatine	female	0.92	1.21	0.27	3.05
19	Creatine	female	1.17	1.15	0.83	7.40
21	Creatine	female	1.17	1.75	1.07	10.67
22	Creatine	female	0.42	0.42	0.42	0.58
25	Creatine	female	0.47	0.44	0.69	1.25
27	Creatine	female	0.15	0.41	0.13	0.62
	avg		**0.72**	**0.90**	**0.57**	**3.93**
	stdev		**0.430113**	**0.559096**	**0.35564**	**4.185257**
2	Placebo	male	0.23	0.65	0.55	0.31
7	Placebo	male	1.39	1.22	0.66	0.43
10	Placebo	male	0.26	0.22	0.23	0.27
14	Placebo	male	1.53	1.01	0.06	0.08
15	Placebo	male	1.04	1.02	0.45	0.52
20	Placebo	male	0.18	0.33	0.14	0.11
23	Placebo	male	0.58	0.81	0.44	0.62
	avg		**0.75**	**0.75**	**0.36**	**0.33**
	stdev		**0.572229**	**0.37453**	**0.223196**	**0.203815**
3	Placebo	female	0.91	1.06	0.56	0.56
9	Placebo	female	1.20	0.67	0.89	0.56
13	Placebo	female	0.24	0.62	0.05	-0.02
18	Placebo	female	1.10	1.19	0.60	0.90
24	Placebo	female	0.09	0.09	0.05	0.06
29	Placebo	female	0.09	0.12	0.07	-0.04
31	Placebo	female	0.45	0.72	0.43	0.48
	avg		**0.58**	**0.64**	**0.38**	**0.36**
	stdev		**0.478816**	**0.420609**	**0.331767**	**0.36078**

APPENDIX D

Correlations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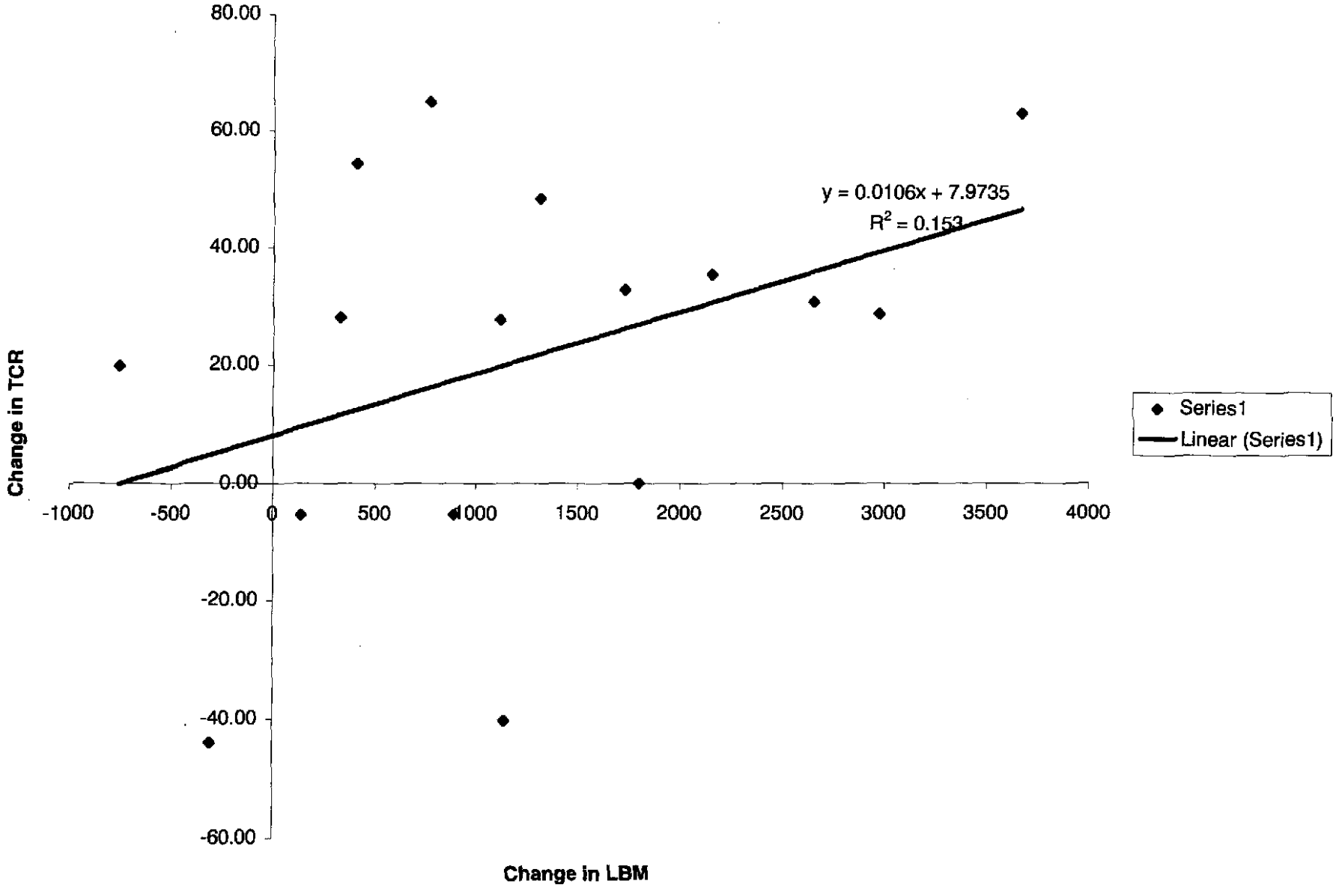
-20
0
20
40
60
80
100
120
140
160
Change in TCr
Change in KE strength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40.00
20.00
0.00
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-60.00
-1000
-500
0
500
1000
1500
2000
2500
3000
3500
4000
y = 0.0106x + 7.9735
R2 = 0.153
Change in TCR
Change in LBM
Series1
Linear (Series1)