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Creatine supplementation and resistance training in vulnerable older women: A randomized double-blind placebo-controlled clinical trial

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ABSTRACT

This study aimed to examine the efficacy of creatine supplementation, associated or not with resistance training, in vulnerable older women. A 24-week, double-blind, randomized, placebo-controlled trial was performed. Sixty subjects were assigned to compose the following groups: placebo (PL), creatine supplementation (CR), placebo with resistance training (PL + RT), and creatine supplementation with resistance training (CR + RT). The subjects were assessed at baseline and after 24 weeks. The primary outcome was muscle strength, as assessed by one-repetition maximum (1-RM) tests. Secondary outcomes included appendicular lean mass, bone mass, biochemical bone markers, and physical function tests. The changes in 1-RM leg press were significantly greater in the CR + RT group (+19.9%) than in the PL (+2.4%) and the CR groups (+3.7%), but not than in the PL + RT group (+15%) ($p = 0.002$, $p = 0.002$, and $p = 0.357$, respectively). The CR + RT group showed superior gains in 1-RM bench press (+10%) when compared with all the other groups ($p \leq 0.05$). The CR + RT group (+1.31%) showed greater appendicular lean mass accrual than the PL (−1.2%), the CR (+0.3%), and the PL + RT groups (−0.2%) ($p \leq 0.05$). The CR and the PL + RT groups experienced comparable gains in appendicular lean mass ($p = 0.62$), but superior to those seen in the PL group. Changes in fat mass, bone mass and serum bone markers did not significantly differ between the groups ($p > 0.05$). In conclusion, creatine supplementation combined with resistance training improved appendicular lean mass and muscle function, but not bone mass, in older vulnerable women. Clinicaltrials.gov: NCT01472393.

1. Introduction

Aging is associated with impaired cognitive function (Bixby et al., 2007), loss of muscle mass, and muscle weakness (Ferri et al., 2003). These aging-related features commonly lead to an impaired ability to perform activities of daily living, increased fall risk (Tinetti et al., 1988), and consequently, mortality (Ruiz et al., 2008).

Even though aging is an inexorable maturational process, malnutrition and physical inactivity are well-known factors that can aggravate muscle function impairment in the elderly. In this regard, exercise training has been considered one of the most important cornerstones in the management of disabilities and co-morbidities secondary to aging, improving physical function and increasing lean mass (Ferri et al., 2003). Furthermore, creatine supplementation has emerged as one of the few efficient dietary interventions capable of attenuating aging-related declines in muscle and cognitive function (Rawson and Venezia, 2011).

Creatine plays an important role in rapid energy provision during muscle contraction involving the transfer of N-phosphoryl group from phosphorylcreatine to ADP in mitochondria to regenerate ATP through a reversible reaction catalyzed by phosphorylcreatine kinase (CK). In addition to its function as a temporal energy buffer, phosphorylcreatine also acts a spatial energy buffer to shuttle high-energy phosphates between mitochondria and cellular ATP utilization sites (Wallimann et al., 1992). Both in younger (Harris et al., 1992) and older (Rawson et al., 2008) individuals, creatine supplementation is able to increase intramuscular creatine and phosphorylcreatine content, thereby enhancing mitochondrial energy provision and consequently muscle strength and function (for a review, see Gualano et al. (2012)). Furthermore, creatine supplementation has been thought to augment lean mass by increasing training volume (Tarnopolsky et al., 2007) as well as by activating satellite cells (Olsen et al., 2006) and specific muscle growth factors (e.g., IGF-1, 4EBP-1) (Deldicque et al., 2005).

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Interestingly, both in vitro and animal studies have revealed a potential role of creatine supplementation in stimulating the development and differentiation of bone cells (Funanage et al., 1992; Gerber et al., 2005). Despite the fact that clinical evidence supporting this hypothesis is still scarce, Louis et al. (2003a) reported increased bone mineral density by 3% and reduced urinary concentrations of cross-linked N-telopeptides of type I collagen (NTx) (i.e., a marker of bone resorption) by 30% in creatine-supplemented patients with Duchenne dystrophy. Furthermore, Candow et al. (2008) demonstrated that creatine supplementation attenuated urinary NTx concentrations by 27% in older males undergoing resistance training. Altogether, these data support the therapeutic application of creatine supplementation as a measure to counteract the decline in muscle strength, lean mass and bone mass secondary to aging.

In fact, a growing number of investigations have demonstrated that in older adults, acute or short-term creatine supplementation, irrespective of exercise training, increases body mass, enhances fatigue resistance, increases muscle strength, and improves the performance of activities of daily living (Gotshalk et al., 2008; Rawson and Clarkson, 2000; Rawson et al., 1999; Stout et al., 2007). Importantly, the combination of creatine supplementation and resistance training seem to act synergistically in offsetting the cluster of disturbances associated with aging to a greater extent than resistance training alone (Candow et al., 2008; Eijnde et al., 2003; Tarnopolsky et al., 2007). Notwithstanding the unequivocal relevance of these findings, the studied volunteers appear to be predominantly physically active, independent adults (Rawson and Venezia, 2011), while little is known regarding the efficacy of creatine supplementation, combined or not with resistance training, in vulnerable older subjects (i.e., those who commonly complain of being "slowed up" or have disease symptoms (Rockwood et al., 2005)).

Thus, the aim of this study was to examine the efficacy of creatine supplementation, associated or not with resistance training, in physically inactive older women with osteopenia or osteoporosis.

2. Materials and methods

2.1. Experimental design

A 24-week, double-blind, randomized, parallel-group, placebo controlled trial was conducted between July 2010 and November 2011 in Sao Paulo (Brazil), according to the guidelines of the Consolidated Standards of Reporting Trials (CONSORT). This study is part of a clinical trial primarily aimed to explore the effects of long-term creatine supplementation on physical function and body composition (in particular, bone mass) in older subjects (registered at clinicaltrials.gov as NCT01472393).

The subjects were randomly assigned (1:1:1:1) to compose either one of the following groups: 1) placebo supplementation (PL; n = 15), 2) creatine supplementation (CR; n = 15), 3) placebo supplementation combined with resistance training (PL + RT; n = 15) or 4) creatine supplementation combined with resistance training (CR + RT; n = 15). We assigned subjects to treatment sequence by using a computer-generated randomization code with a block of four. The subjects from the CR + RT and the PL + RT groups undertook a supervised exercise training program for 24 weeks. The subjects were assessed at baseline (Pre) and after 24 weeks (Post). The primary outcomes were the physical function measures, as assessed by one-repetition maximum (1-RM) tests. Secondary outcomes included bone mass, biochemical bone markers, appendicular lean mass, and physical function tests. Adverse events were recorded throughout the trial and blood parameters (urea, creatinine, alanine aminotransferase, aspartate aminotransferase, and creatine kinase) were assessed before and after the intervention. Possible differences in dietary intake were assessed by three 24-h dietary recalls.

2.2. Subjects

The subjects were recruited into the study by advertising at local health centers. The sample was comprised by postmenopausal women aged ≥ 60 years with osteopenia or osteoporosis (T-score < −1.5 at the lumbar spine, femoral neck or total femur). The exclusion criteria were: participation in physical exercise training over the past 2 years, previous use of creatine supplementation, use of drugs that could affect bone metabolism (e.g., glucocorticoid and bisphosphonates), uncontrolled cardiovascular diseases and/or musculoskeletal disturbances that could preclude exercise participation. All the participants were classified as "apparently vulnerable" (i.e., people who commonly complain of being "slowed up" or have disease symptoms), according to the Canadian Study of Health and Aging (CSHA) clinical frailty scale (Rockwood et al., 2005), which varies from 1 ("very fit") to 7 ("severely ill"), with "apparently vulnerable" being classified as 4.

The study was approved by the Local Ethical Committee and all of the subjects signed the informed consent. All of the procedures were in accordance with the Helsinki Declaration revised in 2008.

2.3. Creatine supplementation protocol and blinding procedure

The subjects from the CR and the CR + RT groups received 20 g/day of creatine monohydrate (Probiotica, Sao Paulo, Brazil) for five days divided into four equal doses, followed by single daily doses of 5 g for the next 23 weeks. The subjects from the PL and the PL + RT groups were given the same dose of dextrose. During the loading phase, supplements were presented in four packages and patients were instructed to ingest the supplement packages at breakfast, lunch, dinner and before bed time. During the maintenance phase, patients consumed the supplement as a single dose during their lunch. They were asked to dissolve the supplements preferably in juice, in order to mask both the low solubility of creatine and the taste of dextrose. The supplement packages were coded so that neither the investigators nor the participants were aware of the contents until completion of the analyses. The supplements were provided by a staff member of our research team who did not have any participation in the data acquisition, analyses, and interpretation. In order to verify the purity of the creatine used, a sample was analyzed by HPLC and purity was established as 99.9%.

2.4. Exercise training

The subjects from the CR + RT and the PL + RT groups engaged in a 24-week supervised resistance training program. Exercise sessions occurred twice-a-week and were monitored by two fitness professionals. The exercise program was performed in an intrahospital gymnasium (Laboratory of Assessment and Conditioning in Rheumatology, School of Medicine, University of Sao Paulo). Resistance training program was comprised of leg press, leg extension, squat, seated row, bench press, lat-pull down, and sit-up exercises. The subjects were required to perform three sets of 8–12 RM, except during the first week, when a reduced volume of two sets of 15–20 RM for each exercise was performed. From the second week on, progression in the absolute exercise load was implemented when the subject could perform more than 12 repetitions on a given exercise set.

2.5. Muscle strength assessments

The subjects underwent two familiarization sessions for strength tests, separated for at least 72 h. Prior to the 1-RM test, two light warm-up sets interspaced for 2 min were performed. Afterwards, the patients had up to five attempts to achieve the 1-RM load, with a three-minute interval between attempts. 1-RM tests were conducted for the leg press and bench press exercises.