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Effect of 12 months of creatine supplementation and whole-body resistance training on measures of bone, muscle and strength in older males

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Abstract

Background: The combination of creatine supplementation and resistance training (10–12 weeks) has been shown to increase bone mineral content and reduce a urinary indicator of bone resorption in older males compared with placebo. However, the longer-term effects (12 months) of creatine and resistance training on bone mineral density and bone geometric properties in older males is unknown. **Aim:** To assess the effects of 12 months of creatine supplementation and supervised, whole-body resistance training on bone mineral density, bone geometric properties, muscle accretion, and strength in older males. **Methods:** Participants were randomized to supplement with creatine ($n = 18$, 49–69 years, 0.1 $g \cdot kg^{-1} \cdot d^{-1}$) or placebo ($n = 20$, 49–67 years, 0.1 $g \cdot kg^{-1} \cdot d^{-1}$) during 12 months of supervised, whole-body resistance training. **Results:** After 12 months of training, both groups experienced similar changes in bone mineral density and geometry, bone speed of sound, lean tissue and fat mass, muscle thickness, and muscle strength. There was a trend ($p = 0.061$) for creatine to increase the section modulus of the narrow part of the femoral neck, an indicator of bone bending strength, compared with placebo. Adverse events did not differ between creatine and placebo. **Conclusions:** Twelve months of creatine supplementation and supervised, whole-body resistance training had no greater effect on measures of bone, muscle, or strength in older males compared with placebo.

Keywords

Bone mineral density, bone strength, lean tissue mass, safety

Introduction

A decrease in bone mineral and bone strength increases the risk of fracture, especially in the hip region (Ebeling et al., 2019). Hip fracture can result in significant disability and loss of functionality (Johnell and Kanis, 2004). It is estimated that by the year 2050, the global prevalence of males experiencing a hip fracture will have increased by 310% (Ebeling et al., 2019) as 25% of hip fractures now occur in males (Potoupnis et al., 2020). Therefore, lifestyle interventions that improve bone mineral and bone strength in older males is important.

The mechanical stimulus from resistance training has a beneficial effect on bone mineral and bone strength, possibly by increasing the rate of bone remodeling (Hong and Kim, 2018). When combined with resistance training, supplementing with creatine (a nitrogenous organic acid) has shown promise for improving some bone measures in older adults (for review see Candow et al., 2019a) whereas creatine supplementation alone has no bone beneficial effects in older adults (Lobo et al., 2015; Sales et al., 2020). There is evidence to suggest that creatine has to be combined with exercise training to maximize its effectiveness. For example, young boys with muscular dystrophy who supplemented with creatine and were independent of a wheelchair for 3 months experienced an increase in bone mineral density and a decrease in bone resorption (urinary excretion of cross-linked N-telopeptides of type I collagen) compared with no change for those who were wheelchair dependent (Louis et al., 2003). Creatine transport into skeletal muscle is greater if exercise is performed prior to

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creatine ingestion (Harris et al., 1992). An increase in intramuscular creatine content from creatine supplementation may improve exercise training capacity (i.e. increase in the number of repetitions performed during a resistance-training session; Chilibeck et al., 2007), which over repeated training sessions could translate into greater muscle accretion (Chrusch et al., 2001). Increased muscle mass from creatine supplementation may increase strain and pull on bone, which over time, could stimulate bone formation (Chilibeck et al., 2005).

We performed a series of studies and showed that creatine supplementation (~ 8 g·d^{-1}) and supervised whole-body resistance training (10–12 weeks) increased upper-limb bone mineral content (Chilibeck et al., 2005) and reduced a urinary marker of bone resorption (cross-linked N-telopeptides of type I collagen; Candow et al., 2008) in older males. However, 8 months of creatine supplementation (~ 8 g·d^{-1}) and supervised, whole-body resistance training had no effect on bone mineral density at clinically relevant sites (i.e. hip and lumbar spine) in older males (Candow et al., 2019c). This study may have been under powered and of too short a duration to improve bone mineral density. Our recent 12-month study in postmenopausal females showed beneficial effects from creatine supplementation in the hip region (i.e. femoral neck bone mineral density) when combined with supervised, whole-body resistance training (Chilibeck et al., 2015). Mechanistically, creatine may influence bone by increasing the metabolic activity, differentiation and mineralization of osteoblast cells involved in bone formation (Gerber et al., 2005), and by reducing urinary indicators of bone resorption (Candow et al., 2008).

Three meta-analyses have been performed involving creatine supplementation and resistance training on muscle mass and strength in older adults. Collectively, creatine supplementation augmented the gains in whole-body lean tissue mass (~ 1.2 kg) and muscle strength (Candow et al., 2014; Chilibeck et al., 2017; Devries and Phillips, 2014), possibly by influencing phosphate metabolism, calcium and muscle protein kinetics, glycogen content, satellite cells, growth factors, inflammation, and oxidative stress (for reviews see Candow et al., 2019b; Chilibeck et al., 2017).

The primary purpose of this investigation was to determine the effects of 12 months of creatine supplementation (0.1 g·kg^{-1}·d^{-1}) and supervised whole-body resistance training on bone mineral density and bone geometric properties in older males. A secondary purpose was to determine the effects of creatine and resistance training on whole-body lean tissue mass, limb muscle thickness, and muscle strength. Based on our previous findings involving creatine and bone (Candow et al., 2008; Chilibeck et al., 2015, 2005) and the meta-analyses results involving creatine and muscle mass and strength in older adults (Candow et al., 2014; Chilibeck et al., 2017; Devries and Phillips, 2014), it was hypothesized that creatine supplementation would have a greater effect on bone mineral, bone geometric properties, muscle accretion, and muscle strength compared with placebo.

Methods

Study Design

The study used a double blind, repeated measures, placebo (control), randomized controlled trial design (Clinical trial identifier: NCT01057680; www.clinicaltrials.gov). Participants were randomized on a 1:1 basis to supplement daily with creatine monohydrate or placebo (corn-starch maltodextrin) during 12 months of supervised, whole-body resistance training. Randomization was performed using a permuted block design with a computer random number generator by a research assistant not involved in any other aspect of the study. All participants performed resistance training as muscle contractions increase creatine uptake into skeletal muscle (Harris et al., 1992). All researchers and those involved in outcome assessments (i.e. densitometry, ultrasound, individuals performing maximal muscle strength tests, data entry, and analyses) or supervision of whole-body resistance training were blinded to group assignments. The multi-site study was approved by the Biomedical Research Ethics Boards at the universities of Saskatchewan and Regina. Participants were informed of the risks and purposes of the study before written consent was obtained. The study complied with the World Medical Association Declaration of Helskinki – Ethical Principles for Medical Research Involving Human Participants. We adhered to the Consolidated Standards of Reporting Trials (CONSORT) guidelines for reporting on randomized clinical trials (Schulz et al., 2010).

Participants

Based on our previous findings showing a decrease in a urinary indicator of bone resorption (cross-linked N-telopeptides of type I collagen) from creatine supplementation and 10 weeks of resistance training in older males compared with placebo (effect size for between-group difference in percent change scores: 1.2; Candow et al., 2008), and assuming that this decrease in bone resorption would be proportional to longer-term (52 weeks) changes in bone mineral, with an alpha level of 0.05 and power of 80%, 24 study participants were required (Statistica 7.0, Chicago IL.). Of the 104 participants who initially volunteered, we were able to randomize 46 eligible males ($\geq$49 years of age) to supplement with creatine or placebo and perform whole-body resistance training for 12 months. Interested participants were excluded if they were already performing resistance training or had pre-existing kidney or liver abnormalities, Crohn's or Cushing's disease, low pre-study creatinine clearance values, history of fragility fractures (defined as fractures resulting from minimal trauma), severe osteoarthritis, had taken corticosteroids, thiazide diuretics, bisphosphonates (i.e. Fosamax, Didrocal, Actonel), parathyroid hormone, or calcitonin within 12 months, or creatine monohydrate supplementation within 6 months prior to the start of the

study. All exclusion criteria were determined by questionnaire except creatinine clearance.

Study settings

The multi-site study was conducted at the University of Saskatchewan in Saskatoon, SK and University of Regina in Regina, SK, Canada. The study commenced in March 2010 and supplementation and resistance training was completed in November 2011.

Intervention

Creatine monohydrate (Rivalus Inc., Canada) and isocaloric placebo (corn-starch maltodextrin; Globe Plus 10 DE Maltodextrin, Univar Canada) were in powder form and similar in color (white), taste (unflavored), texture, and appearance. The purity of the creatine monohydrate was verified by testing in an independent laboratory (DNP International Co. Inc., USA) and established to be 99.2% (free of other contaminants). On resistance-training days (3 days per week, non-consecutive days), participants consumed the supplement (mixed in water, fruit juice or milk) in two equal doses within ~5 min before (0.05 $g \cdot kg^{-1}$) and within ~5 min following (0.05 $g \cdot kg^{-1}$) each training session. On non-training days, participants consumed their supplement in two equal doses (0.05 $g \cdot kg^{-1}$) with food. This creatine ingestion protocol and dosage has been shown to preserve femoral neck bone mineral density and enhance bone geometric properties (i.e. femoral shaft subperiosteal width) and upper-body muscle strength in postmenopausal women, compared with placebo, after 52 weeks of supervised whole-body resistance training (Chilibeck et al., 2015) and increase whole-body lean tissue mass compared with placebo in males (≥50 years of age) (Johannsmeyer et al., 2016). Furthermore, this dosage of creatine did not result in more adverse events compared with placebo in older males (Candow et al., 2008). Adherence with the supplementation protocol was assessed by a compliance log. Upon completion of the study, participants were asked whether they thought they had been administered creatine or placebo.

Resistance-training program

Prior to the start of supplementation, participants were shown how to properly breathe while exercising, use the resistance-training equipment, and perform repetitions to volitional fatigue (defined as the inability to perform the concentric phase of a muscle contraction). Supplementation started on the first day of the resistance-training program, which involved three sessions per week, on non-consecutive days, in private research training facilities in the College of Kinesiology, University of Saskatchewan and in the Faculty of Kinesiology and Health Studies, University of Regina. Exercises included machine-based hack squat, hip (abduction, adduction, flexion, and extension), leg curl, leg extension, low-back extension, chest press, lat-pull down, shoulder press, biceps curl, triceps extension, ankle dorsiflexion and plantarflexion, and dumbbell wrist pronation and supination. Participants were instructed to perform three sets of ~10 repetitions for each exercise at an initial intensity corresponding to approximately 80% of 1-repetition maximum (1-RM; the maximal amount of weight a participant could lift one time) for the hack squat and chest press and at about 10-RM (i.e. the maximal amount of weight that could be lifted 10 times) for the other supplementary exercises. We implemented a higher initial training load for the hack squat and chest press because these were our two primary strength measures. Once three sets of 10 repetitions could be completed for an exercise using a constant training load, the weight was increased and held constant until a subsequent three sets of 10 repetitions could be completed. This progressive strategy (per exercise) was used for the duration of the study. We have previously used this program, in combination with 12 months of creatine supplementation, to positively influence bone mineral density and estimated bone strength in the hip region (femoral neck and shaft) and increase upper-body (chest press) muscle strength in postmenopausal females (Chilibeck et al., 2015). Participants filled out training log sheets during each training session to determine training compliance and training volume. Training volume was calculated by multiplying the load used per exercise by the number of repetitions performed by the number of sets.

Dual energy X-ray absorptiometry

Whole-body lean tissue and fat mass and bone mineral density (whole-body, lumbar spine (L1–L4 vertebrae), proximal femur) was measured by dual energy X-ray absorptiometry in array mode (DXA; QDR Discovery Wi, Hologic, Inc., Bedford, Md.) using QDR software for Windows XP (QDR Discovery). Both universities have the same DXA unit and software. The reproducibility (coefficient of variation (CV); intraclass correlation coefficient (ICC); standard error of measurement (SEM)) of the measurements from previous research (Chilibeck et al., 2015) were as follows: whole-body lean tissue mass (CV: 1.0%, ICC: 0.99; SEM: 0.44 kg), bone mineral density of the whole-body (CV: 0.9%, ICC: 0.98; SEM: 0.01 g/cm^2), lumbar spine (CV: 1.2%, ICC: 0.99; SEM: 0.012 g/cm^2), and proximal femur (CV: 0.9%, ICC: 0.99; SEM: 0.009 g/cm^2).

Bone geometric measures were assessed for three regions (narrow neck, intertrochanteric, and femoral shaft) and included subperiosteal width (SPW; indicates the outer diameter of bone and contributes to section modulus and bending strength of bone), bone cross-sectional area (B-CSA: represents bone mineral content and expresses the amount of bone within a cross-section in relation to cortical equivalent surface area), cross-sectional moment of inertia (CSMI; accounts for the maximum distance of bone mass distribution), and section modulus (Z; accounts for bone mass distribution) (McBreairty et al., 2020). The strength of bone (bending) is associated with CSMI and section

modulus (Chilibeck et al., 2015). The reproducibility of these measures were narrow neck (SPW = CV: 5.3%, ICC: 0.61; SEM: 0.16 cm; B-CSA = CV: 2.6%, ICC: 0.97; SEM: 0.076 cm^2; CSMI = CV: 7.2%, ICC: 0.86; SEM: 0.16 cm^4; Z = CV: 3.5%, ICC: 0.96; SEM: 0.05 cm^3), inter-trochanteric region (SPW = CV: 1.8%, ICC: 0.94; SEM: 0.096 cm; B-CSA = CV: 2.2%, ICC: 0.99; SEM: 0.11 cm^2; CSMI = CV: 4.3%, ICC: 0.97; SEM: 0.52 cm^4; Z = CV: 3.4%, ICC: 0.98; SEM: 0.13 cm^3), and femoral shaft region (SPW = CV: 1.2%, ICC: 0.97; SEM: 0.034 cm; B-CSA = CV: 1.8%, ICC: 0.97; SEM: 0.073 cm^2; CSMI = CV: 3.7%, ICC: 0.98; SEM: 0.12 cm^4; Z = CV: 2.1%, ICC: 0.99; SEM: 0.043 cm^3) (Chilibeck et al., 2015).

Ultrasound

Measurements were performed for the distal radius and tibial shaft (Sunlight, Omnisense 7000 S; Beam Ltd., Petach Tikva, Israel) to determine bone speed of sound (a reflection of bone architecture and density; van den Bergh et al., 2000). The reproducibility from previous research was distal radius (CV: 1.5%, ICC: 0.86; SEM: 62 $m{\cdot}s^{-1}$) and tibial shaft (CV: 0.8%, ICC: 0.78; SEM: 33 $m{\cdot}s^{-1}$) (Chilibeck et al., 2015).

Muscle thickness (elbow and knee flexors/extensors, ankle plantarflexors and dorsiflexors) was determined using B-mode ultrasound (Aloka SSD-500; Tokyo, Japan). The reproducibility from previous research was: elbow flexors (CV: 2.6%, ICC: 0.96; SEM: 0.15 cm), elbow extensors (CV: 2.1%, ICC: 0.88; SEM: 0.18 cm), knee flexors (CV: 2.3%, ICC: 0.99; SEM: 0.14 cm), knee extensors (CV: 2.1%, ICC: 0.99; SEM: 0.15 cm), ankle plantarflexors (CV: 3.1%, ICC: 0.98; SEM: 0.21 cm), and ankle dorsiflexors (CV: 4.0%, ICC: 0.87; SEM: 0.18 cm) (Chilibeck et al., 2015).

Muscle strength

Maximal strength (1-RM) was determined for the upper-body (chest press) and lower-body (hack squat). The reproducibility of these measures from previous research were hack squat (CV: 31.3%, ICC: 0.77; SEM: 22.7 kg), and chest press (CV: 8.2%, ICC: 0.92; SEM: 5.7 kg) (Chilibeck et al., 2015).

Kidney and liver function

Complete blood counts and indicators of kidney (urea, albumin, microalbumin, creatinine clearance, urine protein) and liver function (bilirubin, asparate and alanine aminotransferase, alkaline phosphatase) were determined from blood and urine samples at baseline and 4, 8, and 12 months using procedures as previously described (Chilibeck et al., 2015).

Diet

Habitual dietary intake was determined by having participants fill out 3-day food logs, which were assessed by Nutribase Network Edition software (CyberSoft, Inc., Phoenix, AZ) prior to and following supplementation and training. Physical activity levels, independent of the study, were assessed by the Physical Activity Scale for the Elderly questionnaire (Washburn, 1993) at baseline and at the end of the study.

Adverse events

Adverse events were recorded using adverse event forms, which included a description of the adverse event, its relationship to the intervention (not related, unlikely, possibly, probably, definitely), whether it was serious (i.e. resulted in death, life-threatening, required hospitalization, or resulted in persistent disability) or non-serious, and its intensity (mild, moderate, severe, life-threatening).

Statistical methods

Measures for bone, lean tissue and fat mass, muscle thickness, muscle strength, and diet were assessed by a 2 (groups: creatine (CR) vs. placebo (PLA)) × 2 (time: pre-training vs. post-training) repeated measures analysis of variance, except for training volume, which was assessed at weeks 2, 16, 32, and 52. Adverse events and compliance data were assessed using chi-square analysis. Significance was set a priori at an alpha level of $p < 0.05$.

Results

Participants, training volume and diet

Of the 46 participants who were randomized (CR = 21, PLA = 25), 5 participants in the creatine group and 6 participants in the placebo group withdrew due to health issues or lack of time. Therefore, 35 participants (CR = 16, PLA = 19) completed 12 months of supplementation and resistance training. Of the 11 participants who withdrew, three were able to return for follow-up testing (CR = 18, PLA = 20) and were used in our intent-to-treat analysis (see Figure 1 for a summary of enrollment, allocation and analysis). Baseline data are presented in Table 1. Training compliance (CR: 120/156 sessions completed or 76.9%; PLA: 127/156 or 81.4%; $p > 0.05$) and supplementation compliance were similar between groups (CR: 73%, PLA: 70%; $p > 0.05$). Following the study, we were able to ask 35 participants (CR = 16, PLA = 19) whether they thought they were taking creatine or placebo. Eight participants correctly guessed they were on creatine (50%) and seven participants correctly guessed they were on placebo (36%). There were no differences between groups for the volume of resistance training performed over time (Table 2). There were no changes or differences between groups in total energy, macronutrient, vitamin D, calcium intake (Table 3), or physical activity levels (arbitrary units) over time (CR: pre 196 (127–232), post 180 (141–220); PLA: pre 240 (205–298), post 228 (193–263); $p = 0.59$).

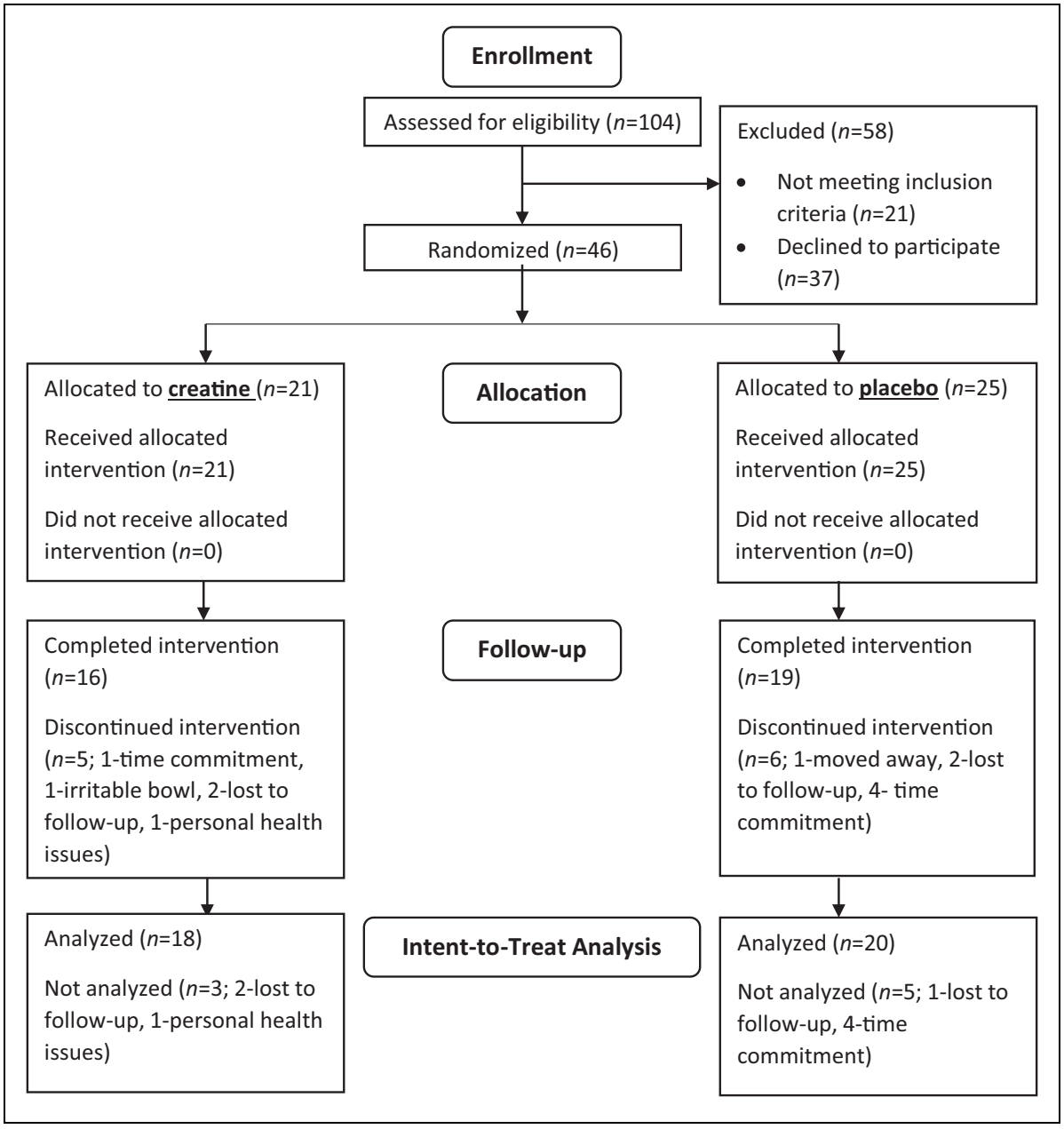

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) diagram outlining research.

Bone measures

There was a time main effect for femoral neck T score (decreased; $p = 0.025$), intertrochanteric Z (increased; $p = 0.047$), and femoral shaft SPW (decreased; $p = 0.009$), B-CSA (increased; $p = 0.013$), CSMI (decreased; $p = 0.015$), and Z (decreased; $p = 0.050$). There was a trend for narrow neck Z to increase in the creatine group relative to the placebo group over time, but this did not reach statistical significance (group × time interaction: $p = 0.061$; Table 4).

Muscle, fat and strength measures

The change in whole-body lean tissue (decreased; $p = 0.007$), appendicular lean tissue (decreased; $p = 0.010$), and fat mass (increased; $p = 0.007$) was similar between groups over time. Both groups experienced an increase in elbow flexor ($p < 0.001$), elbow extensor ($p < 0.001$), ankle dorsiflexor ($p = 0.009$), and total muscle thickness (all muscle groups combined; $p = 0.003$) over time. Regarding muscle strength, there was an increase over time for the hack squat ($p < 0.001$) and chest press ($p = 0.004$), with no significant differences between groups (Table 5).

Adverse events

There were 11 adverse events reported that were possibly related to creatine or placebo ingestion, all of which were classified as mild. Five participants in the creatine group

and two participants in the placebo group reported gastrointestinal issues associated with indigestion, diarrhea, and bloating. Two participants from each group reported cramping. In relation to the resistance-training program, there were 54 adverse events reported involving muscle soreness and joint pain. Forty-three of these were possibly caused, seven were probably caused, and four were definitely caused by the training program. Of the 54 adverse events, 50 were classified as mild and four were considered moderate.

In the creatine group, one participant had high aspartate aminotransferase levels at baseline and another participant had high aspartate aminotransferase levels at 4 and 8 months and high alkaline phosphatase levels at baseline and at 4 and 8 months. Furthermore, 13 participants had high urine creatinine levels at various time points, with five of these participants also having high serum creatinine.

In the placebo group, one participant had high bilirubin levels at 12 months and another participant had low urine creatinine and low creatinine clearance at 12 months. Furthermore, 11 participants had high creatinine levels at various time points, with one of these participants also having high serum creatinine.

Table 1. Baseline data.

	Creatine ($n = 21$)	Placebo ($n = 25$)
Age (years)	58 (6)	56 (5)
Mass (kg)	93 (15)	90 (17)
Height (cm)	177 (6)	176 (5)
Leisure physical activity score (arbitrary units)	196 (78)	240 (98)
Whole-body BMD ($g \cdot cm^{-2}$)	1.220 (0.094)	1.217 (0.123)
Lumbar spine BMD ($g \cdot cm^{-2}$)	1.102 (0.145)	1.079 (0.140)
Total hip BMD ($g \cdot cm^{-2}$)	1.027 (0.125)	1.027 (0.105)
Femoral neck BMD ($g \cdot cm^{-2}$)	0.870 (0.154)	0.843 (0.121)
Narrow neck CSA (cm^2)	3.76 (0.54)	3.63 (0.50)
Narrow neck CSMI (cm^4)	4.50 (0.78)	4.40 (1.23)
Narrow neck Z (cm^3)	2.15 (0.36)	2.11 (0.44)
Narrow neck SPW (cm)	3.84 (0.23)	3.78 (0.34)
Shaft CSA (cm^2)	5.68 (0.67)	5.67 (0.77)
Shaft CSMI (cm^4)	6.39 (1.36)	6.69 (1.71)
Shaft Z (cm^3)	3.61 (0.52)	3.69 (0.74)
Shaft SPW (cm)	3.41 (0.24)	3.46 (0.27)
Intertrochanteric CSA (cm^2)	6.62 (0.90)	6.79 (0.91)
Intertrochanteric CSMI (cm^4)	24.67 (5.49)	25.26 (7.55)
Intertrochanteric Z (cm^3)	6.74 (1.12)	7.02 (1.64)
Intertrochanteric SPW (cm)	6.50 (0.64)	6.23 (0.80)
Distal radius SOS ($m \cdot s^{-1}$)	4090 (123)	4124 (96)
Tibia SOS ($m \cdot s^{-1}$)	3936 (67)	3949 (115)
Whole-body lean tissue mass (kg)	62.5 (7.9)	62.9 (10.1)
Whole-body fat mass (kg)	25.0 (8.1)	23.2 (8.5)
Elbow flexors (cm)	3.98 (0.59)	3.87 (0.61)
Elbow extensors (cm)	3.89 (0.63)	3.66 (0.59)
Knee flexors (cm)	6.26 (1.36)	6.47 (1.16)
Knee extensors (cm)	4.34 (0.74)	4.42 (0.80)
Ankle dorsiflexors (cm)	3.64 (0.87)	3.71 (0.74)
Ankle plantarflexors (cm)	4.52 (2.39)	4.12 (1.96)
All muscle groups combined (cm)	26.63 (4.26)	26.25 (3.83)
Squat 1-RM (kg)	108 (46)	101 (46)
Chest Press 1-RM (kg)	93 (31)	88 (24)
Total energy intake ($kcal \cdot d^{-1}$)	2202 (606)	1912 (396)
Protein ($g \cdot d^{-1}$)	101 (28)	83 (21)
Carbohydrate ($g \cdot d^{-1}$)	271 (73)	225 (46)
Fat ($g \cdot d^{-1}$)	82 (30)	75 (25)
Calcium intake ($mg \cdot d^{-1}$)	788 (103)	821 (153)
Vitamin D intake ($\mu g \cdot d^{-1}$)	21 (5)	20 (8)

Note: Values are means (standard deviation).

Discussion

This was the first study to examine the effects of 12 months of creatine supplementation and supervised, whole-body resistance training in older males. Overall, creatine supplementation had no effect on changes in bone, muscle, or strength. Any positive changes in these variables were therefore related to the resistance-training program.

The only measure that tended to increase with creatine compared with placebo ($p = 0.061$) was narrow neck section modulus, a predictor of bone bending strength (Ebeling et al., 2019). While this was not statistically significant, this trend from creatine supplementation is supported by our previous findings in postmenopausal females who experienced a significant increase in femoral shaft subperiosteal width, another contributor of bone bending strength, with creatine supplementation compared with placebo during an identical 12-month supervised, whole-body resistance training program (Chilibeck et al., 2015). Across these two studies participants performed hack squat, hip abduction, hip adduction, hip flexion, hip extension, leg flexion, leg extension, and low-back extension. All of these exercises directly targeted and placed strain on the hip region, which may have stimulated bone formation when these exercises

Table 2. Comparison of the volume of resistance training (kg) performed at weeks 2, 16, 32 and 52.

	Week 2	Week 16	Week 32	Week 52
Creatine	16,226 (12560–19893)	26,442 (20761–32123)	26,451 (20816–32086)	32,489 (25212–39766)
Placebo	14,834 (11440–18229)	28,403 (23143–33662)	33,597 (28380–38814)	33,016 (26279–39753)

Note: Data are expressed as means (95% confidence intervals); time main effect ($p < 0.001$); group × time interaction ($p = 0.13$).

Table 3. Comparison of total energy, macronutrient, vitamin D and calcium intake following 12 months of creatine or placebo ingestion.

	Creatine		Placebo			
Variable	Baseline	12 months	Baseline	12 months	Time (p)	Group × time (p)
Total energy (kcal)	2212 (1966–2457)	2241 (1761–2720)	1859 (1628–2090)	2171 (1719–2624)	0.32	0.40
Carbohydrates (g)	272 (242–302)	283 (256–309)	222 (193–250)	225 (200–250)	0.39	0.65
Fat (g)	82 (68–95)	83 (75–92)	71 (58–83)	69 (61–78)	0.96	0.68
Protein (g)	100 (88–112)	88 (78–98)	79 (68–91)	81 (71–91)	0.17	0.07
Vitamin D ($\mu g \cdot d^{-1}$)	20 (17–24)	24 (20–27)	19 (16–22)	21 (17–24)	0.23	0.62
Calcium ($mg \cdot d^{-1}$)	785 (714–856)	775 (711–839)	841 (777–906)	844 (787–902)	0.91	0.83

Note: Data are expressed as means (95% confidence intervals)

Table 4. Comparison of bone mineral density, hip geometric measures and speed of sound following 12 months of creatine or placebo ingestion.

	Creatine		Placebo			
Variable	Baseline	12 months	Baseline	12 months	Time (p)	Group × Time (p)
Whole-body BMD (g/cm^2)	1.20 (1.11–1.24)	1.20 (1.16–1.24)	1.21 (1.15–1.27)	1.22 (1.16–1.28)	0.81	0.20
Femoral Neck BMD (g/cm^2)	0.834 (0.770–0.898)	0.841 (0.784–0.898)	0.838 (0.783–0.893)	0.815 (0.766–0.865)	0.46	0.14
Femoral Neck T score	–0.71 (–1.18, –0.24)	–0.82 (–1.27, –0.38)	–0.62 (–1.11, –0.12)	–0.71 (–1.18, –0.25)	0.025	0.83
Trochanter BMD (g/cm^2)	0.741 (0.692–0.789)	0.742 (0.692–0.791)	0.791 (0.749–0.832)	0.790 (0.747–0.832)	1.00	0.84
Wards BMD (g/cm^2)	0.595 (0.521–0.668)	0.600 (0.530–0.670)	0.610 (0.547–0.673)	0.607 (0.547–0.667)	0.91	0.73
Total Hip BMD (g/cm^2)	0.995 (0.947–1.043)	0.996 (0.946–1.046)	1.027 (0.982–1.073)	1.027 (0.980–1.074)	0.95	0.94
Total Hip T score	–0.26 (–0.60, 0.71)	–0.27 (–0.59, 0.47)	0.03 (–0.36, 0.42)	–0.02 (–0.45, 0.40)	0.41	0.32
Lumbar Spine BMD (g/cm^2)	1.097 (1.029–1.164)	1.09 (1.019 –1.154)	1.086 (1.022 –1.152)	1.087 (1.023 –1.152)	0.48	0.36
Lumbar Spine T score	–0.01 (–0.68, 0.65)	–0.12 (–0.70, 0.46)	0.14 (–0.50, 0.79)	0.17 (–0.53, 0.88)	0.58	0.31
Narrow Neck SPW (cm)	3.88 (3.71–4.04)	3.85 (3.66–4.04)	3.77 (3.63–3.91)	3.80 (3.64–3.97)	0.95	0.37
Narrow Neck CSA (cm^2)	3.82 (3.52–4.12)	3.86 (3.56–4.15)	3.62 (3.37–3.88)	3.61 (3.36–3.86)	0.58	0.23
Narrow Neck CSMI (cm^4)	4.71 (4.06–5.36)	4.76 (4.05–5.47)	4.33 (3.78–4.88)	4.09 (3.48–4.70)	0.36	0.17
Narrow Neck Z (cm^3)	2.22 (1.97–2.46)	2.27 (2.02–2.51)	2.07 (1.87–2.28)	2.02 (1.81–2.23)	0.92	0.06
Intertrochanteric SPW (cm)	6.57 (6.23–6.91)	6.67 (6.38–6.97)	6.29 (6.00–6.58)	6.39 (6.14–6.64)	0.19	1.00
Intertrochanteric CSA (cm^2)	6.59 (6.08–7.10)	6.80 (6.39–7.21)	6.68 (6.25–7.11)	6.66 (6.31–7.01)	0.25	0.15
Intertrochanteric CSMI (cm^4)	25.1 (21.2–28.9)	27.2 (24.2–30.3)	24.5 (21.2–27.7)	24.8 (22.2–27.5)	0.079	0.21
Intertrochanteric Z (cm^3)	6.79 (5.96–7.62)	7.20 (6.53–7.88)	6.91 (6.20–7.62)	6.99 (6.42–7.57)	0.047	0.18
Shaft SPW (cm)	3.41 (3.25–3.56)	3.32 (3.16–3.48)	3.45 (3.32–3.58)	3.40 (3.26–3.54)	0.009	0.46
Shaft CSA (cm^2)	5.66 (5.26–6.06)	5.82 (5.43–6.21)	5.57 (5.23–5.91)	5.68 (5.34–6.01)	0.013	0.61
Shaft CSMI (cm^4)	6.49 (5.52–7.46)	6.08 (5.20–6.95)	6.56 (5.74–7.39)	6.36 (5.61–7.10)	0.015	0.40
Shaft Z (cm^3)	3.65 (3.25–4.06)	3.55 (3.20–3.90)	3.63 (3.28–3.97)	3.57 (3.28–3.87)	0.050	0.50
Distal radius SOS ($m \cdot s^{-1}$)	4115.44 (4061.73–4169.15)	4127.61 (4068.21–4187.00)	4124.33 (4077.74–4170.92)	4104.83 (4058.11–4151.55)	0.78	0.23
Tibia SOS ($m \cdot s^{-1}$)	3946.22 (3913.10–3979.34)	3945.00 (3903.61–3986.38)	3941.33 (3882.92–3998.74)	3941.38 (3880.17–4003.38)	0.97	0.93

Note: Data are expressed as means (95% confidence intervals); BMD: bone mineral density; SPW: subperiosteal width; CSA: cross-sectional area; CSMI: cross-sectional moment of inertia; Z: section modulus; SOS: speed of sound.

were performed in conjunction with creatine supplementation. Previous work indicates that creatine has the potential to increase differentiation and mineralization of osteoblast cells involved in bone formation (Gerber et al., 2005) and reduces urinary indicators of bone resorption in older males (Candow et al., 2008). Overall however, our results showed no effect from creatine supplementation on bone mineral density, which is in contrast to our previous study in postmenopausal women, where bone mineral density at the femoral neck was preserved with creatine supplementation compared with placebo (Chilibeck et al., 2015). Other studies with creatine supplementation (no resistance-training intervention) showed no effect on bone mineral density in postmenopausal females (Lobo et al., 2015; Sales et al., 2020).

The lack of overall effect from creatine supplementation and resistance training on bone mineral supports our previous findings in older males. Creatine supplementation ($0.1\ g \cdot kg^{-1} \cdot d^{-1}$) immediately before or after supervised, whole-body resistance training sessions for 8 months produced similar changes in bone mineral density (whole-body, lumbar spine, femoral neck, total hip) compared with placebo in older males (~54 years of age; Candow et al., 2019c). Across both studies, no participant was classified as osteoporotic (based on t-score values), therefore, participants had relatively healthy values for bone mineral density. This may have limited the amount of bone improvement that was possible.

Although there were no statistically significant differences between groups, older males on creatine lost ~1.0 kg

Table 5. Comparison of body composition, muscle thickness and strength measures following 12 months of creatine or placebo ingestion.

	Creatine		Placebo			
Variable	Baseline	12 months	Baseline	12 months	Time (p)	Group × time (p)
Body mass (kg)	92 (85–100)	92 (84–99)	90 (82–99)	91 (83–99)	0.800	0.481
Whole-body LTM (kg)	62.79 (58.87–66.72)	61.89 (58.12–65.66)	62.22 (57.55–66.85)	60.33 (56.03–64.64)	0.007	0.333
Appendicular LTM (kg)	28.70 (27.01–30.40)	28.36 (26.67–30.05)	28.71 (26.82–30.59)	27.62 (25.50–29.74)	0.010	0.165
Whole-body fat mass (kg)	24.65 (20.59–28.72)	25.36 (21.28–29.45)	23.61 (19.24–27.98)	25.62 (21.62–29.62)	0.007	0.178
Elbow flexors (cm)	3.91 (3.60–4.21)	4.15 (3.83–4.46)	3.81 (3.51–4.12)	4.18 (3.84–4.52)	<0.001	0.410
Elbow extensors (cm)	3.87 (3.55–4.20)	4.27 (3.97–4.58)	3.68 (3.39–3.98)	4.07 (3.81–4.33)	<0.001	0.943
Knee flexors (cm)	6.45 (5.93–6.97)	6.69 (6.18–7.19)	6.31 (5.75–6.87)	6.38 (5.76–7.00)	0.170	0.434
Knee extensors (cm)	4.32 (3.99–4.66)	4.43 (4.03–4.83)	4.33 (3.93–4.74)	4.27 (3.92–4.61)	0.816	0.352
Ankle plantarflexors (cm)	4.50 (3.35–5.64)	4.51 (3.37–5.66)	4.01 (3.09–4.92)	3.91 (3.06–4.77)	0.792	0.703
Ankle dorsiflexors (cm)	3.67 (3.22–4.11)	3.98 (3.63–4.32)	3.73 (3.35–4.10)	3.95 (3.61–4.29)	0.009	0.641
Total (cm)	26.74 (24.56–28.93)	28.05 (25.86–30.25)	25.90 (24.09–27.70)	26.78 (24.89–28.66)	0.003	0.535
Squat 1-RM (kg)	111 (87–136)	180 (153–207)	105 (80–129)	181 (154–209)	<0.001	0.650
Chest Press 1-RM (kg)	97 (82–112)	108 (95–112)	92 (77–107)	114 (100–128)	0.005	0.350

Note: Data are expressed as means (95% confidence intervals); LTM: lean tissue mass; Total (cm): all muscle groups combined.

or 1.5% less lean tissue mass compared with placebo. This attenuation in the loss of lean tissue mass from creatine supports the ~0.3 kg greater preservation of lean tissue mass we observed in postmenopausal women supplementing with creatine during an identical resistance-training intervention (Chilibeck et al., 2015). Furthermore, these results align with meta-analyses showing a ~1.2 kg difference in lean tissue mass between creatine and placebo in older adults performing resistance training (Candow et al., 2014; Chilibeck et al., 2017; Devries and Phillips, 2014). Older men on creatine experienced a 1.3% loss in lean tissue mass compared with a 2.8% loss for older men on placebo. Collectively, creatine and resistance training may help preserve lean tissue mass in older adults compared with resistance training alone. Both creatine and placebo groups experienced significant increases in muscle thickness and large improvements in muscle strength, which demonstrates the beneficial effect of resistance training. This may have masked any effects from creatine. We chose to use the hack squat instead of the leg press to determine lower-body muscle strength because we have previously found improvements in hip bone mineral density (BMD) in older adults performing the hack squat (Chilibeck et al., 2013) with no change in hip BMD from the leg press (Chilibeck et al., 2002). However, the hack squat has poor reproducibility (31.3%) compared with the leg press (3%; Chrusch et al., 2001), which may have decreased our ability to detect significant differences in strength between groups over time. We have previously shown that 12 weeks of creatine supplementation during supervised, whole-body resistance training significantly increased leg press strength compared with placebo in older males (Chrusch et al., 2001).

This study had a few limitations. First, initial intramuscular creatine levels, muscle fiber properties, or habitual dietary creatine intake, important variables that influence the responsiveness to creatine supplementation (Candow et al., 2019b), were not assessed, which may have influenced our results. Second, participants did not perform familiarization training sessions with the resistance-exercise equipment prior to the start of the study, which could have increased the amount of neuromuscular learning during the initial phases of training and influenced our results.

In conclusion, this study found no effect from creatine supplementation during supervised, whole-body resistance training on bone mineral density, bone geometric properties, muscle accretion, or muscle strength compared with placebo. Future research should investigate the effects of creatine supplementation and resistance training on more direct measures of bone geometric properties as assessed by methods such as peripheral quantitative computed tomography.

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Author contributions

DGC and PDC formulated the research question, designed the study and performed all statistical analyses. DGC, PDC, JJG, EV, TL, MK and LPJ were involved in the acquisition of data, performing the study and drafting of the manuscript. All authors read and approved the final manuscript.

Declaration of conflicting interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: DGC has conducted industry-sponsored research involving creatine supplementation, received creatine donation for scientific studies and travel support for presentations involving creatine supplementation at scientific conferences. In addition, DGC serves on the Scientific Advisory Board for Alzchem (a company that manufactures creatine).

Ethical approval

The multi-site study was approved by the Biomedical Research Ethics Boards at the universities of Saskatchewan and Regina. The study complied with the World Medical Association Declaration of Helskinki – Ethical Principles for Medical Research Involving Human Participants.

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