Efficacy of Creatine Supplementation and Resistance Training on Area and Density of Bone and Muscle in Older Adults

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ABSTRACT

CANDOW, D. G., P. D. CHILIBECK, J. J. GORDON, and S. KONTULAINEN. Efficacy of Creatine Supplementation and Resistance Training on Area and Density of Bone and Muscle in Older Adults. *Med. Sci. Sports Exerc.*, Vol. 53, No. 11, pp. 2388–2395, 2021. **Purpose:** To examine the efficacy of creatine (Cr) supplementation and any sex differences during supervised whole-body resistance training (RT) on properties of bone and muscle in older adults. **Methods:** Seventy participants (39 men, 31 women; mean age ± standard deviation: 58 ± 6 yr) were randomized to supplement with Cr (0.1 $g \cdot kg^{-1} \cdot d^{-1}$) or placebo (Pl) during RT (3 $d \cdot wk^{-1}$ for 1 yr). Bone geometry (radius and tibia) and muscle area and density (forearm and lower leg) were assessed using peripheral quantitative computed tomography. **Results:** Compared with Pl, Cr increased or maintained total bone area in the distal tibia (Cr, Δ +17 ± 27 mm^2; Pl, Δ −1 ± 22 mm^2; $P = 0.031$) and tibial shaft (Cr, Δ 0 ± 9 mm^2; Pl, Δ −5 ± 7 mm^2; $P = 0.032$). Men on Cr increased trabecular (Δ +28 ± 31 mm^2; $P < 0.001$) and cortical bone areas in the tibia (Δ +4 ± 4 mm^2; $P < 0.05$), whereas men on Pl increased trabecular bone density (Δ +2 ± 2 $mg \cdot cm^{-3}$; $P < 0.01$). There were no bone changes in the radius ($P > 0.05$). Cr increased lower leg muscle density (Δ +0.83 ± 1.15 $mg \cdot cm^{-3}$; $P = 0.016$) compared with Pl (Δ –0.16 ± 1.56 $mg \cdot cm^{-3}$), with no changes in the forearm muscle. **Conclusions:** One year of Cr supplementation and RT had some favorable effects on measures of bone area and muscle density in older adults. **Key Words:** BONE GEOMETRY, MUSCLE DENSITY, FALLS, FRACTURES

Interventions which improve radius and tibial bone geometry and muscle density (MuD) in the surrounding areas may be clinically important for decreasing the risk of falls and fractures in older adults (1,2). We have previously shown that creatine (Cr) supplementation (methylguanidine-acetic acid) during supervised whole-body resistance training (1 yr) decreased the rate of areal bone mineral density (aBMD) loss in the femoral neck and increased femoral shaft subperiosteal width compared with placebo in postmenopausal women (3); however, the same intervention had no effect in men (4). There are no studies investigating the effects of Cr supplementation and resistance training on cortical or trabecular bone structural properties, volumetric bone mineral density, or measures of muscle quality (i.e., MuD), all of which contribute to fracture risk (2).

To date, only two randomized controlled trials have investigated the effects of Cr supplementation (without resistance training) in older adults on cortical and trabecular bone structural properties. Lobo et al (5) found no effect from Cr supplementation (1 $g \cdot d^{-1}$ for 1 yr) when compared with placebo in the radius or tibia in postmenopausal women. A higher dosage and duration of Cr (3 $g \cdot d^{-1}$ for 2 yr) also had no effect in postmenopausal women (6). It is important to note that Cr was not combined with resistance training in either of these previous studies.

Resistance training may stimulate the rate of bone remodeling (7), and Cr may increase bone formation by influencing osteoblast cell activity, differentiation and mineralization (8), and decrease bone resorption as indicated by reduced urinary excretion of cross-linked N-telopeptides of type I collagen (9,10). Furthermore, muscle contractions increase Cr uptake into skeletal muscle (11), which may influence muscle protein kinetics, growth factors, and satellite cells, which are involved in the muscle accretion process (12,13). Increased muscle mass from Cr supplementation may increase strain on bone which over time could stimulate bone accretion (14). However, the effects of Cr supplementation combined with resistance training on cortical and trabecular bone geometry and MuD in older men and women are unknown. Therefore, the purpose was to examine the effects of Cr supplementation and supervised whole-body resistance training on measures of bone geometry in the radius and tibia and muscle area and density of the forearm and lower leg in older adults. As a secondary objective, we determined whether there was a difference between men and women with this intervention, as we previously

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found women increased aBMD in response to Cr and resistance training (3), with no change in men (4). The current study presents pilot data on a subset of participants from these previous studies who had peripheral quantitative computed tomography (pQCT) measurements of bone structural properties and MuD. We hypothesized that older adults supplementing with Cr would experience greater bone and muscle benefits compared with older adults on placebo during a supervised resistance training program.

METHODS

Study design. We have previously described the procedures of the randomized controlled trial (RCT; Clinical trial identifier: NCT01057680; www.clinicaltrials.gov) in detail elsewhere (3,4) where we determined the effects of Cr and supervised resistance training on aBMD in older men and women. The current study presents pilot data on a subset of these participants who underwent measurements with pQCT for evaluation of bone structural properties and MuD. The first participant was enrolled into the study on March 20, 2010, and the last participant was followed up on May 17, 2012. Briefly, participants were randomized to supplement with Cr monohydrate (0.1 $g \cdot kg^{-1} \cdot d^{-1}$) or placebo (0.1 $g \cdot kg^{-1} \cdot d^{-1}$) while they performed 1 yr of supervised whole-body resistance training. All personnel involved in the RCT were blind to group allocations (Cr or placebo). A research assistant was responsible for data entry, with groups coded as A or B. P.D.C. analyzed all coded data and codes were only revealed (to identify Cr and placebo groups) once all analyses were performed. The RCT was approved by the university ethics review board at the University of Saskatchewan. Participants were informed of the risks and purposes of the RCT before their written consent was obtained. The RCT 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 guidelines for reporting on RCT (15).

Participants. Two hundred and ten older adults (≥49 yr; 118 women, 92 men) volunteered to participate in the RCT. Interested participants were excluded if they were already performing supervised whole-body resistance training (>2 $d \cdot wk^{-1}$), were taking corticosteroids or thiazide diuretics, had preexisting kidney or liver abnormalities (includes creatinine clearance values outside normal references ranges), had a history of fragility fractures resulting from minor trauma, had severe osteoarthritis, had consumed dietary supplements containing Cr ≤24 wk or had taken medications ≤1 yr before the start of the RCT that could influence bone biology (includes bisphosphonates, hormone replacement or androgen therapies, selective estrogen receptor modulators, parathyroid hormone, calcitonin). Women were postmenopausal as determined by questionnaire and levels of follicle-stimulating and luteinizing hormone. After exclusion criteria were applied, 53 participants had measures of bone geometry and MuD assessed. Twenty participants in the Cr group (7 men, 13 women), and 21 participants in the placebo group (10 men, 11 women) had low bone mass or osteopenia (defined as a *t*-score ≤ −1.0 for the femoral neck, total hip, and/or lumbar spine). One woman in the Cr group and two women in the placebo group had osteoporosis (defined as a *t*-score ≤ −2.5 for the femoral neck, total hip, and/or lumbar spine).

Intervention. Before the start of the RCT, participants were shown how to properly use the resistance training equipment, perform repetitions to fatigue and fill out their resistance training log booklets. Supervised whole-body resistance training (3 $d \cdot wk^{-1}$ on nonconsecutive days) occurred in a private training facility (i.e., reserved only for research participants). Exercises performed which placed specific strain on regions of the forearm (i.e., radius) and lower leg (i.e., tibia) included dumbbell wrist pronation and supination, Lever machine elbow flexion and ankle plantarflexion (Pulse Fitness Systems; Winnipeg, MB, Canada) and plate-loaded tibia dorsiflexion (Hammer Strength; Life Fitness; Franklin Park, IL). Supplementary exercises performed included Lever machine hack squat, hip (abduction, adduction, flexion, and extension), leg curl, leg extension, low-back extension, chest press, lat-pull

TABLE 1. Baseline data.

	Cr (18 Males, 14 Females)	Placebo (21 Males, 17 Females)
Age (yr)	58 (5)	57 (6)
Mass (kg)	82 (19)	81 (18)
Height (cm)	170 (10)	170 (9)
PASE (arbitrary units)	176 (67)	226 (87)
Distal radius		
ToA (mm^2)	399 (88)	418 (98)
ToC ($mg \cdot mm^{-1}$)	126 (40)	132 (39)
ToD ($mg \cdot cm^{-3}$)	314 (61)	315 (55)
TrA (mm^2)	331 (77)	354 (94)
TrC ($mg \cdot mm^{-1}$)	77 (23)	85 (27)
TrD ($mg \cdot cm^{-3}$)	230 (36)	240 (29)
BSIc ($mg^2 \cdot mm^{-4}$)	41 (20)	43 (19)
Radial shaft		
ToA (mm^2)	147 (31)	150 (34)
CoA (mm^2)	100 (23)	106 (25)
CoC ($mg \cdot mm^{-1}$)	110 (26)	117 (29)
CoD ($mg \cdot cm^{-3}$)	1097 (43)	1104 (29)
SSIp (mm^3)	342 (105)	361 (129)
Distal tibia		
ToA (mm^2)	1233 (180)	1256 (254)
ToC ($mg \cdot mm^{-1}$)	367 (80)	375 (91)
ToD ($mg \cdot cm^{-3}$)	297 (43)	298 (36)
TrA (mm^2)	1124 (168)	1145 (234)
TrC ($mg \cdot mm^{-1}$)	292 (55)	301 (69)
TrD ($mg \cdot cm^{-3}$)	260 (31)	263 (27)
BSIc ($mg^2 \cdot mm^{-4}$)	111 (39)	113 (36)
Tibial shaft		
ToA (mm^2)	645 (118)	664 (118)
CoA (mm^2)	367 (66)	372 (71)
CoC ($mg \cdot mm^{-1}$)	393 (73)	398 (77)
CoD ($mg \cdot cm^{-3}$)	1070 (44)	1069 (25)
SSIp (mm^3)	2830 (725)	2936 (800)
Forearm muscle		
MuA (mm^2)	3826 (1213)	3905 (1169)
MuD ($mg \cdot cm^{-3}$)	74 (1)	74 (2)
Lower leg muscle		
MuA (mm^2)	7507 (1750)	7866 (1728)
MuD ($mg \cdot cm^{-3}$)	69 (3)	69 (4)

Values are means (standard deviation).
PASE, physical activity scale for the elderly; ToA = total bone area; ToC = Total bone content; ToD = Total bone density; TrA = Trabecular bone area; TrC = Trabecular bone content; TrD = Trabecular bone density; BSIc = Bone Strength Index (estimated bone strength in compression); CoA = Cortical bone area; CoC = Cortical bone content; CoD = Cortical bone density; SSIp = Stress-strain index (estimated bone strength in torsion), MuA = Muscle area; MuD = Muscle density.

down, shoulder press, and triceps extension (Pulse Fitness Systems; Winnipeg, MB, Canada). Participants were instructed to perform three sets of approximately 10 repetitions (using a constant load) for each exercise. Once a total of 30 repetitions could be completed, the load 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 resistance training program.

Creatine and placebo ingestion started on the first day of the resistance training program and occurred daily (including nontraining days) for 1 yr. Creatine monohydrate (Rivalus Inc., Canada; purity established to be 99.2% as determined by DNP International Co. Inc., USA) and placebo (corn-starch maltodextrin; Globe Plus 10 DE Maltodextrin, Univar Canada) were in powder form and very similar in appearance and texture. On training days, participants consumed the supplement (mixed in water, fruit juice or milk) in two equal doses (0.05 $g \cdot kg^{-1}$) approximately 5 min before and 5 min after each training session. On nontraining (rest) days, participants consumed their supplement in two equal doses (0.05 $g \cdot kg^{-1}$) with food. Compliance to supplementation (Cr or placebo) and adherence to the resistance training program was assessed by using log booklets. Upon completion of the RCT, participants were asked whether they thought they were taking Cr or placebo during the resistance training program.

pQCT. Detailed procedures for assessing properties of bone and muscle using pQCT (Stratec XCT2000; Medizintechnik GmbH, Pforzheim, Germany) are previously described (16,17). Briefly, baseline and 1-yr scans were performed on the nondominant forearm and ipsilateral lower leg by the same researcher (J.G.). The forearm scans were obtained at the 4% and 65% of the radius length, distal from the reference line (16). The lower leg scans were obtained at 4% and 66% sites of the tibia length (16). We report the following outcomes at the distal sites: total (ToA; mm^2) and trabecular bone areas (TrA; mm^2) and densities (ToD and TrD; $mg \cdot cm^{-3}$), and estimated bone strength (BSIc; $mg^2 \cdot cm^{-4}$) (18,19). We report the following outcomes at the shaft sites: Total (ToA; mm^2) and cortical areas (CoA; mm^2) and cortical density (CoD; $mg \cdot cm^{-3}$) and estimated bone strength (SSIp; mm^3) (18,19). We measured MuD ($mg \cdot cm^{-3}$) and area (mm^2) at the forearm and lower leg (17). Precision errors (CVrms) and related least significant changes in our laboratory range from 1.7% to 6.1% and 4.7% to 16.9% for tibia outcomes; from 0.7 to 2.1%

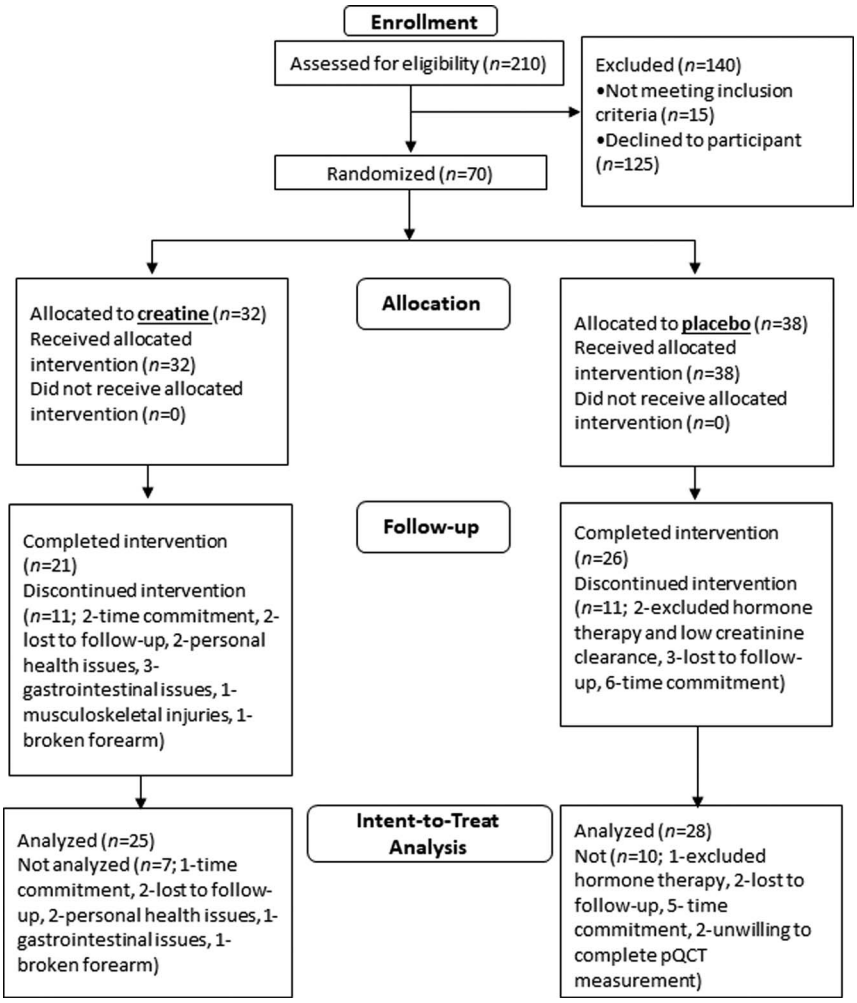

FIGURE 1—Participant flow through RCT.

TABLE 2. Means (95% confidence intervals) at baseline and 1 yr for bone measures of the radius.

	Males				Females						
	Cr (n = 15)		Placebo (n = 16)		Cr (n = 10)		Placebo (n = 12)				
Variable	Baseline	1 yr	Baseline	1 yr	Baseline	1 yr	Baseline	1 yr	Time (P)	Supplement Group–Time (P)	Supplement Group–Sex–Time (P)
Distal radius											
ToA (mm^2)	489 (451–527)	490 (453–527)	516 (479–553)	507 (472–543)	359 (312–406)	377 (332–423)	371 (328–414)	375 (339–417)	0.48	0.28	0.83
ToC ($mg \cdot mm^{-1}$)	157 (144–169)	157 (144–169)	170 (159–182)	169 (157–181)	101 (87–116)	105 (90–121)	103 (90–117)	103 (89–117)	0.50	0.27	0.45
ToD ($mg \cdot cm^{-3}$)	323 (297–349)	324 (298–349)	335 (310–361)	339 (314–364)	285 (253–317)	279 (248–311)	283 (254–312)	277 (248–305)	0.54	0.82	0.79
TrA (mm^2)	410 (367–454)	413 (373–453)	435 (393–478)	424 (385–463)	310 (256–363)	329 (280–378)	328 (279–377)	334 (289–379)	0.52	0.30	0.96
TrC ($mg \cdot mm^{-1}$)	98 (87–109)	99 (89–109)	109 (99–120)	107 (98–117)	66 (52–79)	72 (59–84)	73 (61–86)	75 (64–86)	0.40	0.34	0.87
TrD ($mg \cdot cm^{-3}$)	241 (228–255)	243 (228–257)	252 (239–265)	255 (241–269)	212 (195–229)	215 (197–233)	225 (210–240)	226 (209–242)	0.060	0.71	0.30
BSIc ($mg^2 \cdot mm^{-4}$)	51 (44–58)	52 (45–58)	58 (51–64)	58 (51–65)	29 (21–38)	30 (21–39)	30 (22–37)	29 (21–37)	0.81	0.49	0.65
Radial shaft											
ToA (mm^2)	171 (158–182)	170 (159–181)	174 (163–184)	173 (163–184)	121 (108–135)	122 (109–135)	124 (112–137)	125 (112–137)	0.95	0.66	0.93
CoA (mm^2)	117 (110–125)	116 (109–124)	124 (117–131)	124 (117–131)	85 (76–94)	84 (75–93)	86 (77–94)	86 (78–94)	0.34	0.44	0.82
CoC ($mg \cdot mm^{-1}$)	128 (119–137)	128 (119–137)	137 (128–145)	136 (128–145)	94 (83–104)	93 (83–104)	95 (85–105)	95 (85–104)	0.20	0.94	0.92
CoD ($mg \cdot cm^{-3}$)	1096 (1077–1115)	1097 (1077–1116)	1102 (1084–1120)	1101 (1082–1119)	1110 (1088–1132)	1114 (1091–1137)	1108 (1088–1129)	1103 (1082–1124)	0.91	0.21	0.45
SSIp (mm^3)	422 (382–461)	421 (382–460)	439 (402–476)	449 (412–485)	255 (208–301)	256 (209–302)	264 (221–307)	266 (223–308)	0.27	0.27	0.33

ToA = total bone area; ToC = Total bone content; ToD = Total bone density; TrA = Trabecular bone area; TrC = Trabecular bone content; TrD = Trabecular bone density; BSIc = Bone Strength Index (estimated bone strength in compression); CoA = Cortical bone area; CoC = Cortical bone content; CoD = Cortical bone density; SSIp = Stress-strain index (estimated bone strength in torsion).

FIGURE 2—Change from baseline to 1 yr for distal tibia area. Error bars represent standard deviations. Individual data are represented by the open circles. *Cr group experienced a greater change compared with the placebo group (P = 0.031). Difference between groups for posttraining means = 20 (95% CI: −109 to 149) mm^2.

and 1.9% to 5.8% for radius outcomes; and from 1.2% to 3.7% and 3.3% to 10.2% for muscle outcomes, respectively (17,18).

Statistics. A 2 (groups: Cr vs placebo) × 2 (sex: men vs women) × 2 (time: baseline vs 1 yr) repeated-measures ANOVA was performed on all variables to determine differences over time. Bonferroni *post hoc* tests were performed when significant interactions were found. Significance was set *a priori* at an alpha level of 0.05. Values are presented as means ± standard deviation or means and 95% confidence intervals.

RESULTS

Baseline data are presented in Table 1. The flow of participants through the study is presented in Figure 1. Following the study, we were able to ask 52 participants (Cr = 27, Pl = 25) whether they thought they were taking Cr or placebo. Seventeen participants correctly guessed they were on Cr (63%), and 15 participants correctly guessed they were on placebo (60%).

There were no significant changes in any bone measure for the radius (P > 0.05) (Table 2). At the distal tibia, there was a group–time interaction for ToA (P = 0.031) with the Cr group experiencing a greater change (Δ + 17 ± 27 mm^2) compared with the placebo group (ToA: Δ −1 ± 22 mm^2) (Fig. 2). There were also group–sex–time interactions for TrA (P = 0.034), ToD (P = 0.013), and TrD (P = 0.031) (Table 3). Men on Cr experienced a significant increase in TrA over time (Δ + 28 ± 31 mm^2; P < 0.01). When Bonferroni *post hoc* analysis was applied, there were no significant changes across men or women in the Cr or Pl groups for ToD. Trabecular bone density significantly increased in men on placebo (Δ + 2 ± 2 $mg \cdot cm^{-3}$; P < 0.01). There was a time main effect for trabecular bone content (+3 ± 7 $mg \cdot mm^{-1}$; P = 0.007) (Table 3).

At the tibial shaft, there was a group–time interaction for ToA (P = 0.032), where individuals supplementing with Cr

TABLE 3. Means (95% confidence intervals) at baseline and 1 yr for bone measures of the tibia.

	Males				Females						
	Cr (n = 15)		Placebo (n = 16)		Cr (n = 10)		Placebo (n = 12)				
Variable	Baseline	1 yr	Baseline	1 yr	Baseline	1 yr	Baseline	1 yr	Time (P)	Supplement Group–Time (P)	Supplement Group–Sex–Time (P)
Distal tibia											
ToA (mm^2)	1414 (1327–1501)	1437 (1353–1539)	1465 (1383–1546)	1460 (1381–1538)	1098 (995–1201)	1105 (1006–1205)	1108 (1010–1206)	1113 (1010–1206)	0.028	**0.031**	0.052
ToC ($mg \cdot mm^{-1}$)	425 (403–448)	428 (406–450)	451 (430–472)	452 (431–473)	300 (274–327)	300 (274–327)	314 (289–339)	313 (288–338)	0.25	0.29	0.91
ToD ($mg \cdot cm^{-3}$)	305 (287–322)	302 (284–319)	310 (294–327)	312 (296–328)	274 (253–295)	272 (252–293)	284 (264–304)	281 (262–301)	0.03	0.08	**0.013**
TrA (mm^2)	1285 (1189–1381)	1313* (1220–1407)	1319 (1229–1409)	1314 (1226–1401)	1027 (913–1141)	1035 (925–1146)	1030 (921–1139)	1039 (934–1144)	0.015	0.039	**0.034**
TrC ($mg \cdot mm^{-1}$)	336 (314–359)	344 (322–366)	351 (330–371)	352 (331–372)	253 (226–279)	254 (228–280)	262 (237–287)	264 (239–288)	0.007	0.12	0.12
TrD ($mg \cdot cm^{-3}$)	265 (252–277)	264 (252–277)	268 (256–279)	270* (258–281)	246 (231–261)	246 (231–261)	254 (240–269)	254 (239–268)	0.71	0.12	**0.031**
BSIc ($mg^2 \cdot mm^{-4}$)	130 (118–141)	129 (118–141)	140 (130–151)	142 (131–152)	82 (69–96)	82 (69–95)	90 (77–103)	89 (76–102)	0.75	0.58	0.09
Tibial shaft											
ToA (mm^2)	743 (704–782)	746 (706–785)	747 (711–784)	743 (707–780)	558 (513–603)	555 (510–600)	572 (529–615)	566 (523–609)	0.023	**0.032**	0.31
CoA (mm^2)	417 (396–439)	421** (399–443)	413 (393–433)	414 (394–434)	321 (296–345)	317 (292–341)	321 (297–344)	319 (295–342)	0.53	0.78	**0.035**
CoC ($mg \cdot mm^{-1}$)	445 (421–470)	447 (422–472)	444 (421–467)	444 (421–467)	346 (318–374)	342 (314–371)	343 (315–370)	342 (315–369)	0.27	0.42	**0.02**
CoD ($mg \cdot cm^{-3}$)	1067 (1048–1086)	1062 (1043–1081)	1074 (1056–1091)	1071 (1054–1088)	1081 (1059–1102)	1082 (1061–1103)	1068 (1048–1089)	1074 (1054–1094)	0.95	0.14	0.63
SSIp (mm^3)	3435 (3193–3678)	3439 (3206–3673)	3486 (3261–3712)	3467 (3250–3685)	2280 (2004–2556)	2238 (1972–2503)	2295 (2031–2558)	2290 (2037–2544)	0.05	0.62	0.053

All values set in boldface are significant.

*$P \leq 0.01$ vs prevalue (Bonferroni *post hoc* of supplement group–sex–time interaction); **$P < 0.05$ vs prevalue (Bonferroni *post hoc* of supplement group–sex–time interaction).

ToA = total bone area; ToC = Total bone content; ToD = Total bone density; TrA = Trabecular bone area; TrC = Trabecular bone content; TrD = Trabecular bone density; BSIc = Bone Strength Index (estimated bone strength in compression); CoA = Cortical bone area; CoC = Cortical bone content; CoD = Cortical bone density; SSIp = Stress-strain index (estimated bone strength in torsion).

FIGURE 3—Change from baseline to 1 yr for tibial shaft area. Error bars represent standard deviations. Individual data are represented by the open circles. *Cr group experienced a greater change compared to the placebo group (P = 0.032). Difference between groups for posttraining means = 6 (95% CI: −61 to 72) mm^2.

maintained ToA over time (Δ 0 ± 9 mm^2) compared with a decrease for those on placebo (Δ − 5 ± 7 mm^2) (Fig. 3). There were group–sex–time interactions for CoA (P = 0.035) and cortical bone content (CoC) (P = 0.020) (Table 3). Men on Cr experienced a significant increase in CoA (Δ + 4 ± 4 mm^2; $P < 0.05$). Bonferroni *post hoc* analysis showed no significant changes within men or women on Cr or placebo for CoC. There was a time main effect for SSIp (mm^3) (Δ − 14 ± 54 mm^3; P = 0.05) (Table 3).

There was a group–time interaction for lower leg muscle MuD (P = 0.016) with the Cr group experiencing an increase in MuD (Δ + 0.83 ± 1.15 $mg \cdot cm^{-3}$) compared with those on placebo (Δ − 0.16 ± 1.56 $mg \cdot cm^{-3}$) (Fig. 4). There were time main effects for forearm muscle area (MuA) (Δ + 109 ± 174 mm^2; increasing; $P < 0.001$) and lower leg MuA (Δ − 254 ± 460 mm^2; $P < 0.001$), with no other differences (Table 4).

DISCUSSION

This was the first RCT to investigate the combined effects of Cr supplementation and supervised whole-body resistance training on cortical and trabecular structural properties of bone and MuD in older adults. Creatine supplementation increased total bone area in the distal tibia and tibial shaft, as well as MuD in the lower leg compared to placebo. Furthermore, men on Cr increased trabecular and cortical bone areas in the tibia compared with men on placebo, whereas men on placebo increased trabecular bone density compared with men on Cr. These preliminary results are important because in addition to larger and stronger bones, higher density in calf and thigh muscles have been associated with reduced risk of falls and fractures in older adults (1,2,16,20).

Changes in bone geometry such as increased bone cross-sectional area are associated with increased bone strength (21)

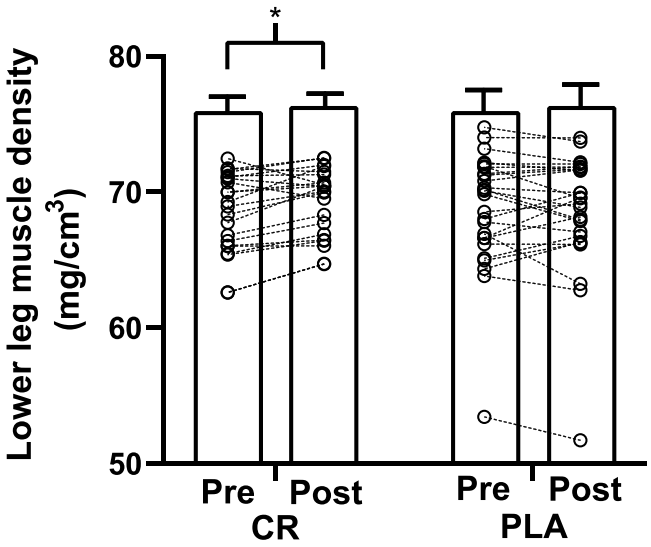

FIGURE 4—Change from baseline to 1 yr for lower leg MuD. Error bars represent standard deviations. Individual data are represented by the open circles. *Cr group experienced a greater change compared to the placebo group (P = 0.016). Difference between groups for posttraining means = 0.8 (95% CI: −1.4 to 3.0) mg·cm^{-3}.

and reduced fracture risk in older adults (2). Tibial fractures, which often occur more frequently in men compared with women (22), decrease mobility and functionality and cause substantial burden to the health care system through increased hospitalization, homecare, and physical and occupational rehabilitation therapies (23). Older adults who have experienced a fracture have significantly lower MuD (indicative of reduced muscle quality) in muscles attached to the tibia compared with those with no history of fracture (16). Low MuD in the lower leg is also associated with higher risk of falls in older adults (1). Our findings of increased bone area in the tibia and increased MuD of the lower leg may, therefore, have clinical relevance for prevention of future falls and fractures.

The favorable effects from Cr supplementation on tibial bone geometry suggest that Cr may be most effective when combined with resistance training as other studies have failed to find beneficial effects from Cr alone (without resistance training) on tibial bone geometry in postmenopausal women compared with placebo (5,6). There is evidence that the combination of Cr and resistance training produces greater gains in muscle accretion compared with Cr alone in older adults (24). Muscle acts as a pulley and bone as a lever and the mechanical forces applied to bone during muscle contractions may result in net bone formation over time (25). We have previously shown that upper-limb muscle accretion from 12 wk of Cr supplementation and resistance training correlates with upper-limb bone mineral accrual in older men (14). Mechanistically, Cr may have a favorable effect on bone by increasing osteoblast cell activity (8) and reducing bone resorption (urinary excretion of cross-linked N-telopeptides of type I collagen; NTx) (9,10). In addition to the importance of resistance training and the muscle–bone interaction, we used a

TABLE 4. Means (95% confidence intervals) at baseline and 1 yr for muscle measures in the forearm and lower leg.

	Males				Females						
	Cr (n = 14)		Placebo (n = 16)		Cr (n = 10)		Placebo (n = 12)				
Variable	Baseline	1 yr	Baseline	1 yr	Baseline	1 yr	Baseline	1 yr	Time (p)	Supplement Group–Time (P)	Supplement Group–Sex–Time (P)
Forearm											
MuA (mm^2)	4810 (4483–5137)	4991 (4690–5291)	4826 (4520–5132)	4914 (4633–5195)	2661 (2274–3048)	2782 (2426–3138)	2956 (2603–3309)	3000 (2675–3324)	0.000048	0.085	0.88
MuD (mg·cm^{-3})	73 (73–74)	74 (73–75)	74 (73–75)	74 (73–75)	74 (73–75)	74 (73–75)	74 (73–75)	74 (73–75)	0.087	0.92	0.33
Lower leg											
MuA (mm^2)	8672 (8036–9309)	8570 (7922–9218)	8679 (8110–9249)	8352 (7773–8931)	6198 5501–6896)	6023 (5313–6732)	7071 6406–7736)	6680 (6003–7356)	0.00059	0.11	0.97
MuD (mg·cm^{-3})	67 (65–69)	68 (66–70)	69 (67–71)	69 (67–71)	70 (68–73)	71 (68–73)	69 (66–71)	68 (66–70)	0.16	**0.016**	0.65

All values set in boldface are significant.
MuA = Muscle area; MuD = Muscle density.

APPLIED SCIENCES

higher dosage of Cr (0.1 $g \cdot kg^{-1} \cdot d^{-1}$ or ~8 $g \cdot d^{-1}$) compared to that of Lobo et al (5) (1 $g \cdot d^{-1}$) and Sales et al (6) (3 $g \cdot d^{-1}$). We have previously shown that 0.1 $g \cdot kg^{-1} \cdot d^{-1}$ of Cr supplementation increased femoral shaft subperiosteal width and decreased the rate of aBMD loss in the femoral neck and bone resorption (NTx) in older adults compared with those on placebo (3,9).

The small increases in trabecular and cortical bone area in the tibia from Cr supplementation in older men may be clinically relevant. Larger bone area in the tibia is associated with greater bone strength (failure load, moment, and stiffness; 21) and protection against future fractures (2,26). This is important because tibial fractures typically occur more frequently in men compared with women (22) and result in physical limitations (23). Interpretation of these small, within-group changes in bone area warrants caution, however, as the observed changes were comparable to the precision errors (CV_{rms}) and below the least significant changes in tibia total, trabecular, and cortical areas (18). These pilot findings, together with our estimates of the monitoring time intervals for pQCT outcomes, indicate a need for longer-term interventions when assessing bone adaptation in older adults (17,18).

The lack of change in bone measures in the radius may also be related to our resistance training program design. Only two exercises (dumbbell wrist pronation and supination) were performed that directly targeted the forearm and may not have been sufficient to stimulate bone accretion in the radius over time. We have previously shown that the addition of medicine ball toss-and-catch and dumbbell forearm curl to a similar resistance training program used in the present study had favorable effects on measures of radius in postmenopausal women (27).

Older adults who supplemented with Cr experienced a significant increase in lower-leg MuD compared with those on placebo which may be important because low MuD is an independent risk factor for falls (1) and disability in older adults (28). Specifically, every $mg \cdot cm^{-3}$ decrease in MuD is associated with a 17% increase in the odds of reporting a fall in older adults (1). It is well established that Cr supplementation influences several variables involved in the muscle accretion process (i.e., muscle protein kinetics, growth factors, satellite cells (12,13,29) and may decrease body fat in older adults (30), which may explain our positive findings.

There were limitations to this RCT not already discussed. First, the small sample size likely decreased our ability to detect significant changes in some of our bone and muscle measures over time. The pilot results presented in the current study can provide important information for a larger future RCT. The most important of our bone-related pQCT results for prevention of fracture is predictive bone strength at the distal radius (i.e., BSIc) (16). Considering the change for the Cr and placebo groups of 0.6 and −0.2, with a common standard deviation of 4.3 $mg^2 \cdot mm^{-4}$, we would require a sample size of 455 per group to realize a statistical difference at $P = 0.05$ with 80% power. Alternatively, the most important muscle-related pQCT result for prevention of falls and fracture is lower leg MuD (1,20). Considering the change in Cr and placebo groups of 0.82 and −0.16, with a common standard deviation of 1.46 $mg \cdot cm^{-3}$, we would require a sample size of 36 per group to realize a statistical difference at $P = 0.05$ with 80% power. Second, no measure of forearm or lower-leg muscle strength was performed. However, we have previously reported in these older adults that Cr supplementation significantly increased chest press strength in older women compared with older women on placebo (3), with no differences found between older men and older women on Cr or placebo for hack squat strength (3,4). Third, serum indicators of bone formation (i.e., osteocalcin, procollagen 1 N-propeptides), bone formation inhibition (i.e., sclerostin) and urinary indicators of bone resorption (i.e., type 1 collagen C-telopeptides, cross-linked N-telopeptides) were not assessed which limits our ability to determine how Cr supplementation and resistance training influenced measures of bone turnover. We have, however, shown that Cr supplementation reduces cross-linked N-telopeptides compared with placebo in older adults (9). Finally, without measuring muscle and bone Cr levels, we are unable to determine the individual responsiveness to Cr supplementation over time.

In summary, 1 yr of Cr supplementation (0.1 $g \cdot kg^{-1} \cdot d^{-1}$) and supervised resistance training increased total bone area in the tibia and lower leg MuD in older adults. Future research should determine the mechanistic effects of Cr supplementation during resistance training on muscle and bone properties using advanced imaging tools and test the efficacy of the combined intervention on measures of muscle strength, bone turnover and the incidence of falls and fractures in older adults.

Results of this study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation.

The results of the present study do not constitute endorsement by the American College of Sports Medicine.

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