Creatine Supplementation for Older Adults

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Sarcopenia, defined as age-related reduction in muscle mass, strength, and physical performance, is associated with other age-related health conditions such as osteoporosis, osteosarcopenia, sarcopenic obesity, physical frailty, and cachexia. From a healthy aging perspective, lifestyle interventions that may help overcome characteristics and associated comorbidities of sarcopenia are clinically important. One possible intervention is creatine supplementation (CR). Accumulating research over the past few decades shows that CR, primarily when combined with resistance training (RT), has favourable effects on aging muscle, bone and fat mass, muscle and bone strength, and tasks of physical performance in healthy older adults. However, research is very limited regarding the efficacy of CR in older adults with sarcopenia or osteoporosis and no research exists in older adults with osteosarcopenia, sarcopenic obesity, physical frailty, or cachexia.

sarcopenia osteoporosis osteosarcopenia frailty cachexia

1. Introduction

Sarcopenia refers to age-related reductions in muscle strength (dynapenia), muscle mass (quantity), relative strength (strength per unit of muscle mass), muscle quality (architecture and composition), and/or physical performance (i.e., tasks of functionality) [1]. Sarcopenia typically occurs in 8–13% of adults ≥60 years of age [2] and is associated with other age-related health conditions such as osteoporosis, osteosarcopenia, sarcopenic obesity, physical frailty, and cachexia. Annually, muscle mass decreases by 0.45% in men and by 0.37% in women, but these decrements climb to 0.9% for men and to 0.7% for women starting in their seventh decade [3]. The age-related decrease in muscle strength, which is a strong predictor of poor health outcomes (mobility disability, falls, fractures, and mortality) in older adults [1], occurs more rapidly (2–5 fold faster) than the reduction in lean (muscle) mass [4].

From a global health perspective, the World Health Organization established a code (ICD-10-CM; M62.84) for sarcopenia as a means for better diagnosis, assessment, and treatment of the condition. While several definitions and subcategories of sarcopenia exist, the European Working Group on Sarcopenia in Older People (EWGSOP) defines individuals with low muscle strength (as assessed by grip-strength or chair-stand test) as having probable sarcopenia; those with low muscle strength and low muscle quantity (as assessed by dual energy X-ray absorptiometry, magnetic resonance imaging and spectroscopy, computed tomography, bioelectrical impedance, creatine dilution, and/or muscle biopsy) as having confirmed sarcopenia; and those with low muscle strength, low muscle quantity, and poor physical performance (as assessed by gait speed, short physical performance battery test, timed-up-and-go test, or 400 m walk test) as having severe sarcopenia [1]. Sarcopenia is classified as primary

when its etiology is age dependent whereas secondary sarcopenia is influenced by age and/or other factors such as physical inactivity and undernutrition [1]. Contributing factors to the pathophysiology of sarcopenia include changes in neuromuscular function, skeletal muscle morphology and architecture, protein kinetics, hormonal regulation, growth factors and satellite cells, vascularization, inflammation, mitochondrial function, nutrition, and physical activity [1][3][4]. From a healthy aging perspective, interventions that may help overcome characteristics and associated comorbidities of sarcopenia (i.e., osteoporosis, osteosarcopenia, sarcopenic obesity, physical frailty, and cachexia) are clinically important.

Accumulating research over the past few decades shows that creatine supplementation (CR), primarily when combined with resistance training (RT), has some favourable effects on muscle accretion and bone mineral density, bone and muscle strength, and tasks of functionality in older adults (for reviews, see Candow et al. [5], Chilibeck et al. [6], Forbes et al. [7], Gualano et al. [8], and Kreider et al. [9]). However, research is very limited regarding the efficacy of CR in older adults with sarcopenia or osteoporosis and no research exists in older adults with osteosarcopenia, sarcopenic obesity, physical frailty, or cachexia. Therefore, the purpose of this narrative review is (1) to evaluate and summarize current research involving CR, with and without RT, on properties of muscle and bone in older adults and (2) to provide a rationale and justification for future research involving CR in older adults with osteosarcopenia, sarcopenic obesity, physical frailty, or cachexia.

2. Potential of Creatine Supplementation for Sarcopenia

The majority of aging research involving CR has focused on measures of muscle accretion and strength in response to RT. Studies published to date involving >600 older adults (>48 years of age) show divergent results, possibly because of methodological differences across studies (Table 1). We have previously reviewed the majority of these studies in detail elsewhere [5][8][10][11][12][13]. Most studies (n = 16) involved healthy older adults, whereas 4 studies involved older adults with knee osteoarthritis, osteopenia or osteoporosis, type II diabetes, or chronic obstructive pulmonary disease (COPD). The results are equivocal regarding the efficacy of CR on measures of muscle accretion and strength, with half of the studies showing greater gains from CR vs. placebo (PLA) and the other half showing similar effects between the two interventions during an RT program. Individual studies typically lack adequate statistical power to detect small changes in muscle accretion and strength from CR over time, and the responsiveness to CR in older adults may be influenced by initial resting PCr levels in different muscle regions, changes in type II muscle fibre size and quantity, and habitual dietary intake of creatine [12]. To overcome the limitations of low statistical power and high variability amongst older adult populations, three meta-analyses have been performed to determine the efficacy of CR (≥3 g/day) vs. PLA during an RT program (≥7 weeks) on measures of muscle accretion and strength [6][14][15]. Collectively, these meta-analyses showed that the combination of CR and RT augmented muscle accretion (≈1.2 kg), and upper- and lower-body strength more than PLA and RT in older adults. Mechanistically, the greater increase in muscle accretion and strength from CR may be related to its ability to influence phosphate metabolism, calcium and glycogen regulation, cellular swelling, muscle protein signaling and breakdown, myogenic transcription factors and satellite cells, growth factors (i.e., IGF-1 and myostatin), inflammation, and oxidative stress (for reviews, see Candow et al. [5], Chilibeck et al. [6], Gualano et al. [8], and

Kreider et al. [9]). Upon CR cessation, the gains in muscle accretion and strength seem to persist for up to 12 weeks when RT is maintained in older adults [16].

Table 1. Summary of studies examining creatine and resistance training on muscle outcomes in older adults.

First Author, Year	Population	Supplement Dose	Resistance Training	Duration	Outcomes
Aguiar et al. 2013 [17]	*N* = 18; healthy women; Mean age = 65 y	CR (5 g/day), PLA	RT = 3 x/wk	12 wks	CR ↑ gains in fat-free mass (+3.2%), muscle mass (+2.8%), 1 RM bench press, knee extension, and biceps curl compared to PLA
Alves et al. 2013 [18]	*N* = 47; healthy women, Mean age = 66.8 y (range: 60–80 y)	CR (20 g/day for 5 days, followed by 5 g/day thereafter), PLA with and without RT	RT = 2 x/wk	24 wks	↔1 RM strength compared to RT + PLA
Bemben et al. 2010 and Eliot et al. 2008 [19] [20]	*N* = 42; healthy men; age = 48–72 y	CR (5 g/day), PRO (35 g/day), CR + PRO, PLA	RT = 3 x/wk	14 wks	↔lean tissue mass, 1 RM strength
Bermon et al. 1998 [21]	*N* = 32 (16 men, 16 women); healthy; age = 67–80 y	CR (20 g/day for 5 days followed by 3 g/day), PLA	RT = 3 x/wk	7.4 wks (52 days)	↔lower limb muscular volume, 1- and 12-repetitions maxima, and isometric intermittent endurance
Bernat et al. 2019 [22]	*N* = 24 healthy men; age = 59 ± 6 y	CR (0.1 g/kg/day), PLA	High-velocity RT = 2 x/wk	8 wks	↔muscle thickness, physical performance, upper-body muscle strength; CR ↑ leg press strength, total lower body strength
Brose et al. 2003 [23]	*N* = 28 (15 men, 13 women); healthy; age: men = 68.7,	CR (5 g/day), PLA	RT = 3 x/wk	14 wks	CR ↑ gains in lean tissue mass and isometric knee extension strength; ↔ type 1, 2 a, 2 x muscle fibre area

First Author, Year	Population	Supplement Dose	Resistance Training	Duration	Outcomes
	women = 70.8 y				
Candow et al. 2008 [24]	*N* = 35; healthy men; age = 59–77 y	CR (0.1 g/kg/day), CR + PRO (PRO: 0.3 g/kg/day), PLA	RT = 3 x/wk	10 wks	CR ↑ muscle thickness compared to PLA. CR ↑1 RM bench press ↔ 1 RM leg press
Candow et al. 2015 [25]	*N* = 39 (17 men, 22 women); healthy; age = 50–71 y	CR (0.1 g/kg) before RT, CR (0.1 g/kg) after RT, PLA	RT = 3 x/wk	32 wks	CR after RT ↑ lean tissue mass, 1 RM leg press, 1 RM chest press compared to PLA
Candow et al. 2020 [26]	*N* = 38; healthy men; age = 49–67 y	CR (On training days: 0.05 g/kg before and 0.05 g/kg after exercise) + 0.1 g/kg/day on non-train-ing days (2 equal doses) or PLA	RT = 3 x/wk	12 months	↔lean tissue mass, muscle thickness, or muscle strength
Chilibeck et al. 2015 [27]	*N* = 33; healthy women; Mean age = 57 y	CR (0.1 g/kg/day), PLA	RT = 3 x/wk	52 wks	↔lean tissue mass and muscle thickness gains between groups; ↑ relative bench press strength compared to PLA.
Chrusch et al. 2001 [28]	*N* = 30; healthy men; age = 60–84 y	CR (0.3 g/kg/d for 5 days followed by 0.07 g/kg/day), PLA	RT = 3 x/wk	12 wks	CR ↑ gains in lean tissue mass; CR ↑1 RM leg press, 1 RM knee extension, leg press endurance, and knee extension endurance; ↔ 1 RM bench press or bench press endurance.
Cooke et al. 2014 [29]	*N* = 20; healthy men; age = 55–70 y	CR (20 g/day for 7 days followed by 0.1 g/kg/day on training days)	RT = 3 x/wk	12 wks	↔lean tissue mass, 1 RM bench press, 1 RM leg press
Deacon et al. 2008 [30]	*N* = 80 (50 men, 30	CR (22 g/day for 5 day followed by	RT = 3 x/wk	7 wks	↔lean tissue mass or muscle strength

First Author, Year	Population	Supplement Dose	Resistance Training	Duration	Outcomes
	women); COPD; age = 68.2 y	3.76 g/day), PLA			
Eijnde et al. 2003 [31]	*N* = 46; healthy men; age = 55–75 y	CR (5 g/day), PLA	Cardiorespiratory + RT = 2–3 x/wk	26 wks	↔lean tissue mass or isometric maximal strength
Gualano et al. 2011 [32]	*N* = 25 (9 men, 16 women); type 2 diabetes; age = 57 y	CR (5 g/day), PLA	RT = 3 x/wk	12 wks	↔lean tissue mass
Gualano et al. 2014 [33]	*N* = 30; "vulnera-ble" women; Mean age = 65.4 y	CR (20 g/day for 5 days; 5 g/day thereafter), PLA with and without RT	RT = 2 x/wk	24 wks	CR + RT ↑ gains in 1RM bench press and appendicular lean mass compared to PLA + RT
Johannsmeyer et al. 2016 [34]	*N* = 31 (17 men, 14 women); healthy; age = 58 y	CR (0.1 g/kg/day), PLA	RT = 3 x/wk	12 wks	CR ↑ gains in lean tissue mass; ↔ 1RM strength and endurance; CR attenuated magnitude increase in time to complete balance test compared to PLA
Neves et al. 2011 [35]	*N* = 24 (postmen-opausal women with Knee osteo-arthritis); Age = 55–65 y	CR (20 g/day for 1 week, followed by 5 g/day), PLA	RT = 3 x/wk	12 wks	CR ↑ gains in limb lean mass. ↔ 1RM leg press
Pinto et al. 2016 [36]	*N* = 27 (men and women); healthy; age = 60–80 y	CR (5 g/day), PLA	RT = 3 x/wk	12 wks	CR ↑ gains in lean tissue mass; ↔ 10 RM bench press or leg press strength
Smolarek et al. 2020 [37]	*N* = 26 (5 men, 21 women); long-term care residence;	CR (5 g/day), PLA	RT = 2 x/wk	16 wks	CR ↑ dominant and non-dominant handgrip strength

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an mass, adjusted for height and weight [39]), CR (20 g/day for 5 days + 5 g/day for 23 weeks) during supervised whole-body RT (3 sets of 8–12 repetitions, 2 days per week) eliminated the sarcopenia classification in two of the women [33].

First Author, Year	Population	Supplement Dose	Resistance Training	Duration	Outcomes
	age = 68.9 ± 6.8 y				

/day) and

Regarding physical performance (functionality), two meta-analyses of older adults demonstrated that CR in conjunction with RT resulted in greater improvements in sit-to-stand performance when compared to RT (plus PLA) alone [5][15]. These findings are of clinical relevance given that improving sit-to-stand performance may reduce the risk of falls in older adults [40].

CR = creatine; PRO = protein; RM = repetition maximum; ↑ = significant greater; ↔ = no difference between conditions; wk = weeks; y = years; g = grams; kg = kilograms.

Independent of RT, research is mixed regarding the effectiveness of CR on aging muscle, with 5 studies showing greater effects from CR vs. PLA and 5 studies showing similar effects between the two interventions (for review, see Forbes et al. [41]). While it is difficult to compare results across studies, these inconsistent findings may be related to the CR protocol and/or dosage used. The majority of studies that found beneficial effects from CR incorporated a CR loading phase (20 g/day) or used a high relative daily dosage of creatine (0.3 g/kg/day), whereas several of the studies that failed to observe beneficial effects did not use these strategies.

In summary, CR (≥3 g/day) and RT (≥7 weeks; primarily whole-body routines) can improve some measures of muscle accretion, strength, and physical performance in older adults. Independent of RT, a CR loading phase and/or high relative daily dosage of creatine (≥0.3 g/kg/day) may be required to produce some muscle benefits in older adults. It is unknown whether the combination of CR and RT provides greater fitness benefits compared to CR alone. Furthermore, the effects of CR in sarcopenic older adults is relatively unknown. No research exists regarding the efficacy of CR in older adults with inborn creatine synthesis deficiencies involving arginine–glycine amidinotransferase (AGAT), guanidinoacetate methyl transferase (GAMT), solute carrier 6 (SLC6AB), or CT1 (creatine transporter). Future research should investigate the effects of CR, with and without RT, in older clinical populations with possible musculoskeletal disorders and creatine synthesis/transporter deficiencies.

3. Potential of Creatine Supplementation for Osteoporosis

Osteoporosis refers to age-related loss of bone mineral density (BMD) and architecture [42] that increases bone fragility and the risks of falls and fractures [43]. There are 8 published studies that have examined the combined effects of CR and RT on properties of bone in older adults, with only 3 of these studies showing greater effects from creatine compared to PLA (Table 2). In healthy older men, 12 weeks of CR (loading phase: 0.3 g/kg/day for 5 days; maintenance phase: 0.07 g/kg/day for an additional 79 days) and supervised whole-body RT increased upper-limb bone mineral content (assessed by dual energy X-ray absorptiometry [DXA]) compared to PLA [44]. Additional work in healthy older men showed that 10 weeks of CR (0.1 g/kg/day) and supervised whole-body RT decreased the urinary excretion of cross-linked N-telopeptides of type I collagen (indicator of bone resorption) compared to PLA [24]). Most recently, Chilibeck et al. [27] showed that CR (0.1 g/kg/day) and supervised whole-body RT for 52 weeks attenuated the rate of bone mineral loss in the femoral neck (assessed by DXA) (Figure 1) and increased femoral shaft subperiosteal width (indicator of bone bending strength) in postmenopausal women compared to PLA.

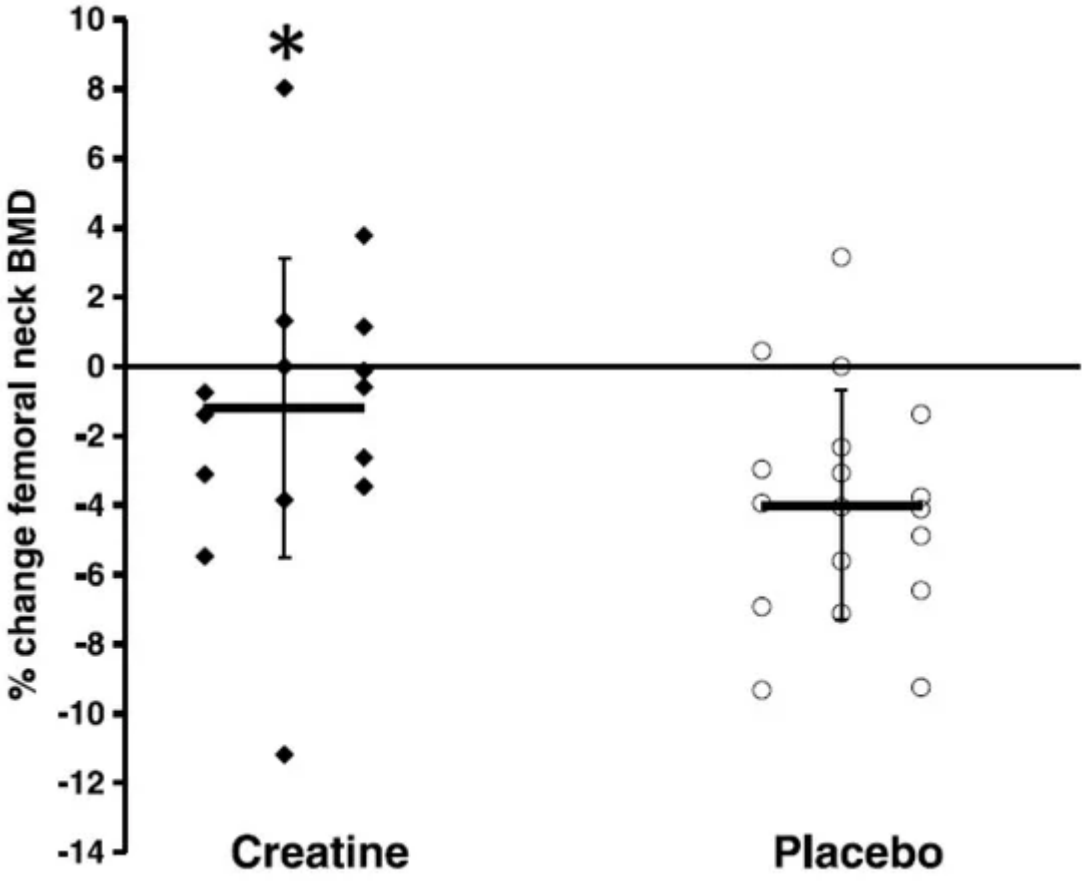

Figure 1. Relative changes in femoral neck bone mineral density (BMD). “Closed diamonds” represent changes for individual creatine group participants, and “open circles” represent placebo group participants. The “horizontal bars” represent the group means, and the “vertical bars” represent the SD. * Creatine participants lost significantly less BMD at the femoral neck compared with placebo participants ($p < 0.05$). (Reproduced with permission from Chilibeck et al. 2015 [27]).

Table 2. Study characteristics and outcomes of research examining the influence of creatine with a resistance training program on bone.

First Author, Year	Study Population	Intervention	Duration	Outcomes
Brose et al. 2003 [23]	*N* = 28; healthy (15 men, 13 women); age ≥ 65 y (men = 68.7 y, women = 70.8 y)	RCT; CR + RT, PLA + RT. CR = 5 g/day; RT = 3 x/wk	14 wks	↔on osteocalcin
Candow et al. 2008 [24]	*N* = 35; older men (age: 59–77 y)	RCT; CR + PRO + RT; CR + RT, PLA + RT; CR = 0.1 g/kg/day; RT = 3 x/wk	10 wks	CR ↓ NTx
Candow et al. 2019 [5]	*N* = 39; healthy (17 men; 22 women); age ≥ 50 y (mean ~55 y)	RCT; CR-Before + RT, CR-After + RT, PLA + RT; CR = 0.1 g/kg/day; RT = 3 x/wk	8 mths	↔BMD and BMC of the whole-body, limbs, femoral

First Author, Year	Study Population	Intervention	Duration	Outcomes
				neck, lumbar spine, and total hip
Candow et al. 2020 [26]	*N* = 38; healthy men; age = 49–67 y	RCT; CR + RT, PLA + RT; CR = 0.1 g/kg/day; RT = 3 x/wk	12 mths	↔ BMD and geometry, bone speed of sound; CR ↑ (p = 0.06) section modulus of the narrow part of the femoral neck
Chilibeck et al. 2005 [44]	*N* = 29; older men (71 y).	RCT; CR + RT, PLA + RT; CR = 0.3 g/kg/day for 5 days followed by 0.07 g/kg/day for the remaining; RT = 3 x/wk	12 wks	↑ arm BMC greater in the CR group com-pared to PLA; ↔ between groups for whole-body and leg BMD
Chilibeck et al. 2015 [27]	*N* = 33; postmenopausal women; age: 57 ± 6 y	RCT; PLA + RT, CR + RT; CR = 0.1 g/kg/day (0.05 g/kg provided immediately before and 0.05 g/kg after training on training days and with two meals on non-training days); RT = 3 x/wk	12 mths	CR attenuated rate of femoral neck BMD loss compared to PLA and CR ↑ femoral shaft subperiosteal width; ↔ between groups on all other outcome measures
Gualano et al. 2014 [33]	*N* = 60; older vulnerable women (age: 66 y)	RCT; PLA, CR, PLA + RT, CR + RT; CR = 20 g/day for 5 days followed by 5 g/day for the remaining; RT = 2 x/wk	24 wks	↔bone mineral and serum bone markers between groups
Pinto et al. 2016 [36]	*N* = 32; healthy, non-athletic men and women between 60–80 y	RCT; PLA + RT, CR + RT; CR = 5 g/day; RT = 3 x/wk. Muscle groups (i.e., upper and lower body) alternated between training days, 1.5 x/wk per muscle group	12 wks	↔BMD and BMC of all assessed sites between groups

[23]

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formation) and type 1 collagen C-telopeptide (CTX; indicator of bone resorption) compared to PLA in older women. In addition, 12 weeks of CR (5 g/day) and supervised whole-body RT had no greater effect on measures of BMD or content (assessed by DXA) compared to PLA in healthy older adults [36]. Similarly, Candow et al. [45] was unable to find greater effects from CR (0.1 g/kg/day) and 12 weeks of supervised whole-body RT on measures of bone mineral density and content (assessed by DXA) compared to PLA in healthy older adults. Most recently, Candow et al. [26] failed to show a significant greater effect from 52 weeks of CR (0.1 g/kg/day) and supervised whole-body RT on measures of BMD, bone geometric properties (assessed by DXA and ultrasound) in older men compared to PLA.

There are only three studies that have investigated the effects of CR alone (no exercise training stimulus) on properties of aging bone. In postmenopausal women with osteopenia or osteoporosis, 24 weeks of CR (loading phase: 20 g/day for 5 days; maintenance phase: 5 g/day for an additional 23 weeks) had no effect on measures of BMD (whole-body, lumbar, total femur, and femoral neck; assessed by DXA) or serum markers of bone turnover (CTX, P1NP) compared to PLA [33]. In two additional studies involving postmenopausal women, CR (1 g/day for 52 weeks) had no effect on measures of BMD (assessed by DXA), bone microarchitecture (assessed by high-

resolution peripheral quantitative computed tomography (HR-pQCT)), CTX, or P1NP compared to PLA [46]. Increasing the dosage of creatine to 3 g/day for an additional 52 weeks (104 weeks in total) also had no effect on the same bone measures in postmenopausal women. Furthermore, creatine had no effect on the number of falls or fractures experienced [47].

Collectively, the vast majority of studies show no greater effect from CR, with and without RT, on properties of bone in older adults. In the few studies that did show beneficial effects, CR was combined with supervised whole-body RT. Importantly, no study showed any detrimental effect from CR on bone mineral or geometry. The combined effects of CR and RT on reducing the risk and incidence of falls and fractures in older adults is largely unknown. Bone tissue typically takes a long time (i.e., several months) to turnover [48], especially in older adults [49]. Future research should investigate the longer-term effects (i.e., ≥2 years) of CR, with and without RT, on properties of bone mineral and geometry and risk of falls and fractures in older adults.

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