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Creatine supplementation for older adults: Focus on sarcopenia, osteoporosis, frailty and Cachexia

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ABSTRACT

Sarcopenia refers to the age-related reduction in strength, muscle mass and functionality which increases the risk for falls, injuries and fractures. Sarcopenia is associated with other age-related conditions such as osteoporosis, frailty and cachexia. Identifying treatments to overcome sarcopenia and associated conditions is important from a global health perspective. There is evidence that creatine monohydrate supplementation, primarily when combined with resistance training, has favorable effects on indices of aging muscle and bone. These musculoskeletal benefits provide some rationale for creatine being a potential intervention for treating frailty and cachexia. The purposes of this narrative review are to update the collective body of research pertaining to the effects of creatine supplementation on indices of aging muscle and bone (including bone turnover markers) and present possible justification and rationale for its utilization in the treatment of frailty and cachexia in older adults.

1. Introduction

Sarcopenia, commonly defined as the age-related decrease in strength, muscle mass and functionality, is associated with osteoporosis, frailty and cachexia [1]. Furthermore, sarcopenia increases the risk of falls, injuries, fractures and premature mortality [2]. The etiology and pathophysiology leading to sarcopenia is multifactorial and includes alterations in skeletal muscle protein turnover and balance, endocrinological processes, neurophysiology, inflammation, vascularization, and mitochondrial function [3]. Sarcopenia occurs in 5–17 % of community-dwelling aging adults and 14–85 % in those residing in long-term care facilities [4]. With estimates that by the year 2050 there will be 1.5 billion adults ≥65 years of age [5], the prevalence of sarcopenia will continue to rise for the foreseeable future. Therefore, identifying treatments to overcome sarcopenia and associated age-related conditions is critically important from a global health perspective.

We have previously discussed and summarized the small body of research showing some favorable effects of creatine monohydrate supplementation on indices of aging muscle and bone (for reviews see [1,6,7]). Overall, creatine (primarily when combined with resistance training) has been shown to increase measures of muscle accretion, strength and functionality [6–10]. Creatine has also been shown to increase bone area [11,12] and strength [13], attenuate the rate of bone mineral loss [13] and influence bone turnover by reducing the urinary excretion of cross-linked N-telopeptides (NTx) or C-telopeptides of type I collagen (CTx) in older adults [14]. Assessing bone turnover markers (i.e., NTx, CTx) are clinically relevant as they provide important information regarding the bone remodeling process and predict the risk of osteoporotic fracture in older adults [15]. Based on these musculoskeletal benefits, it is highly plausible that creatine may be an effective intervention to treat frailty (characterized by muscle weakness) and cachexia (characterized by rapid muscle wasting). However, research in these clinical areas is minimal.

The purposes of this narrative review are to: (1) expand on our previous publications [1,6,7] and further update the collective body of research pertaining to the effects of creatine supplementation on indices

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of aging muscle and bone (including bone turnover markers) and (2) present possible justification and rationale for its utilization in the treatment of frailty and cachexia in older adults.

2. Aging muscle

2.1. Creatine supplementation and resistance training

Resistance training is the most effective strategy to attenuate the age-related decrease in strength, muscle mass and function, warranting its ample recommendations to offset characteristics of sarcopenia [16]. Accumulating research over the past few decades shows that the addition of creatine supplementation to a resistance training program has some favorable effects on measures of muscle accretion and performance in older adults compared to resistance training alone (Table 1). However, results from most studies performed are limited due to low sample sizes and inadequate statistical power. To overcome these limitations and determine with greater probability whether creatine supplementation and resistance training is superior to placebo and resistance training in older adults, several meta-analyses have been performed.

In this respect, DeVries and Phillips [8] were the first to summarize the literature and analyze 10 randomized placebo-controlled trials investigating whether creatine supplementation could enhance the

Table 1
Study characteristics and outcomes of research examining the influence of creatine with a resistance training program on muscle in older adults.

Study	Participant characteristics; sample size	Dosing strategy	Resistance training frequency	Intervention length	Results
Alves et al., [100]	Healthy women (mean age: 66.8 y, range: 60–80 y); $N = 47$	CR 20 g/d for 5 d followed by 5 g/d for the remainder or PLA	2 d/wk	24 wks	↔ 1RM strength
Aguiar et al., [101]	Healthy women (mean age: 65 y); $N = 18$	CR 5 g/d or PLA	3 d/wk	12 wks	CR ↑ gains in fat-free mass, muscle mass, 1RM bench press, knee extension, and biceps curl
Bemben et al. [21] and Eliot et al. [22]	Healthy men (age: 48–72 y); $N = 42$	CR 5 g/d or PLA	3 d/wk	14 wks	↔ lean tissue mass, 1RM strength
Bermon et al., [111]	Healthy older adults (age: 67–80 y); $N = 32$	CR 20 g/d for 5 d followed by 3 g/d for remainder or PLA	3 d/wk	7.4 wks (52 days)	↔ lower limb muscular volume, 12-repetitions maxima, isometric intermittent endurance
Bernat et al., [112]	Healthy men (age: 59 ± 6 y); $N = 24$	CR 0.1 g/kg/d or PLA	High-velocity RT 2 d/wk	8 wks	↔ muscle thickness, physical performance, upper body muscle strength. CR ↑leg press strength, total lower body strength
Brose et al. [34]	Healthy older adults (men mean age: 68.7 y, women mean age: 70.8 y); $N = 28$	CR 5 g/d or PLA	3 d/wk	14 wks	CR ↑ lean tissue mass, isometric knee extension strength; ↔ type 1, 2a, 2× muscle fiber area
Candow et al. [14]	Healthy men (age: 59–77 y); $N = 35$	CR 0.1 g/kg/d or PLA	3 d/wk	10 wks	CR ↑muscle thickness CR ↑1RM bench press ↔ 1RM leg press
Candow et al., [113]	Healthy older adults (age: 50–71 y); $N = 39$	CR 0.1 g/kg/d before or after RT or PLA	3 d/wk	32 wks	CR after RT ↑ lean tissue mass, 1RM leg press, 1RM chest press compared to PLA
Candow et al., [1,11,12,63]	Healthy men (age: 49–67 y); $N = 38$	CR 0.1 g/kg/d on non-training days and 0.05 g/kg before and 0.05 g/kg after RT or PLA	3 d/wk	12 months	↔ lean tissue mass, muscle thickness, 1RM strength
Candow et al., [1,11,12,63]	Healthy older adults (age: 58 ± 6 y); $N = 70$	CR 0.1 g/kg/d or PLA	3 d/wk	12 months	CR ↑ lower leg muscle density
Chilibeck et al. [13]	Healthy women (mean age: 57 y); $N = 33$	CR 0.1 g/kg/d or PLA	3 d/wk	52 wks	↔ lean tissue mass, muscle thickness. CR ↑ relative bench press strength
Chrusch et al. [102]	Healthy men (age: 60–84 y); $N = 30$	CR 0.3 g/kg/d for 5 d followed by 0.07 g/kg/d for the remainder or PLA	3 d/wk	12 wks	CR ↑ lean tissue mass. CR ↑1RM leg press, 1RM knee extension, leg press endurance, knee extension endurance. ↔ 1RM bench press or bench press endurance
Cooke et al. [103]	Healthy men (age: 55–70 y); $N = 20$	CR 20 g/d for 7 d followed by 0.1 g/kg/d on training d or PLA	3 d/wk	12 wks	↔ lean tissue mass, 1RM bench press, 1RM leg press
Deacon et al. [104]	Older adults with COPD (mean age: 68.2 y); $N = 80$	CR 22 g/d for 5 d followed by 3.76 g/d or PLA	3 d/wk	7 wks	↔ lean tissue mass or muscle strength
Eijnde et al., [105]	Healthy men (age: 55–75 y); $N = 46$	CR 5/d or PLA	Cardiorespiratory + RT = 2–3 d/wk	26 wks	↔ lean tissue mass or isometric maximal strength
Gualano et al., [106]	Type 2 diabetics (mean age: 57 y); $N = 25$	CR 5 g/d or PLA	3 d/wk	12 wks	↔ lean tissue mass
Gualano et al., [55]	Vulnerable women (mean age: 65.4 y); N = 30	CR 20 g/d for 5 d followed by 5 g/d for the remainder	2 d/wk	24 wks	CR ↑ 1RM bench press, appendicular lean mass
Hass et al., [107]	Older adults with idiopathetic Parkinson's disease (mean age: 62 y); N = 20	CR 20 g/d for 5 d followed by 5 g/d for the remainder or PLA	2 d/wk	12 wks	CR ↑ chest press strength, sit to stand; ↔ Leg extension 1RM, muscular endurance
Johannsmeyer et al., [108]	Healthy older adults (mean age: 58 y); $N = 31$	CR 0.1 g/kg/d or PLA	3 d/wk	12 wks	CR ↑ lean tissue mass, 1RM strength in men only
Neves et al., [109]	Postmenopausal women with Knee osteoarthritis (age: 55–65 y); N = 24	CR 20 g/d for 1 week followed by 5 g/d for the remainder or PLA	3 d/wk	12 wks	CR ↑ limb lean mass. ↔ 1RM leg press
Pinto et al. [57]	Healthy older adults (age: 60–80 y); $N = 27$	CR 5 g/d or PLA	3 d/wk	12 wks	CR ↑lean tissue mass. ↔ 10-RM bench press or leg press strength
Smolarek et al., [110]	Long-term care residence (age: 68.9 ± 6.8 y); $N = 26$	CR 5 g/d or PLA	2 d/wk	16 wks	CR ↑ dominant and non-dominant handgrip strength

CR: creatine; PLA: placebo; d: day; y: years; wks: weeks; ↑ significant increase; ↔ no differences between creatine and placebo; RT: resistance training; RM: repetition maximum.

beneficial effects of resistance training on body composition, strength and functional performance in over 300 older adults (≥55 years). Results showed that the combination of creatine supplementation and resistance training significantly improved whole-body lean mass (+1.33 kg), leg press (weighted mean difference [WMD]: 3.25 kg) and chest press strength (WMD: 1.74 kg) and functional performance (assessed by the 30-s sit-to-stand chair test; WMD: 0.43) compared to placebo and resistance training. The improvement in sit-to-stand performance from creatine has further been corroborated by an expanded meta-analysis performed by Candow et al. [6].

Following this initial review, Candow et al. [17] conducted a similar meta-analysis involving over 400 participants (>48 years). In line with the results of Devries and Phillips [8], the combination of creatine and resistance training resulted in greater gains in lean mass (+0.94 kg) and chest press strength (standardized mean difference [SMD]: 0.42 kg) compared to placebo and resistance training. Conversely, no greater effect from creatine and resistance training was observed on leg press strength.

Conclusions from these initial meta-analyses were encouraging, but results were also somewhat equivocal, particularly in relation to the influence of creatine supplementation on lower body strength, an outcome that is clinically relevant for maintaining activities of daily living among individuals suffering from sarcopenia. In both analyses, it was concluded that the results should be carefully interpreted based on the small number of studies performed, as well as the substantial heterogeneity regarding the study populations and the characteristics of the training and creatine supplementation protocols. To overcome these possible limitations, Chilibeck et al. [7] performed the largest and most comprehensive meta-analysis to date involving 22 studies and over 700 older adults (≥50 years). Results showed that the combination of creatine supplementation and resistance training significantly improved measures of lean mass (+1.37 kg) and chest-press (SMD: 0.35) and leg-press strength (SMD: 0.24) compared to placebo and resistance training. To further validate the efficacy of creatine, when studies that combined creatine with other compounds such as whey protein and conjugated linoleic acid (CLA) were excluded in the analysis, creatine and resistance training was still superior to placebo for increasing measures of lean mass and strength.

Since the publication these papers [7,8,17], two additional meta-analyses involving creatine supplementation in older adults have been performed. In 2021, Forbes et al. [9] showed that the combination of creatine supplementation (independent of dosage) and resistance training significantly increased measures of lean mass (+1.32 kg) and chest-press (SMD: 0.28) and leg-press strength (SMD: 0.20). compared to resistance training alone. When creatine dosage was considered in the analyses, only studies that included a creatine loading phase (≥20 g/day for the first 5–7 days) generally resulted in significant improvements in strength compared to placebo. Furthermore, supplementing with creatine only on resistance training days was an effective strategy to augment measures of lean mass (+1.73 kg) and chest-press (SMD: 0.58) and leg-press strength (SMD: 0.44) compared to ingesting placebo on training days. These unique findings have application for the design of effective creatine ingestion protocols to improve lean mass and strength in older adults. Most recently, a small-scale meta-analysis involving only post-menopausal females (≥60 years) showed that creatine and resistance training (≥24 weeks in duration) significantly increased upper-body (SMD: 0.41) and lower-body strength (SMD: 0.44). However, creatine had no greater effect on measures of lean mass over time [10].

Since the publication of these meta-analyses, an additional paper has been published. In healthy older males and postmenopausal females, the combination of creatine supplementation (~8 g/day) and 1 year of supervised whole-body resistance training had favorable effects on lower-leg muscle density (Δ +0.83 ± 1.15 mg·cm^{-3}), as assessed by peripheral quantitative computed tomography, compared to those on placebo (Δ -0.16 ± 1.56 mg·cm^{-3}) [11]. These results may be clinically relevant because increased lower-limb muscle density is associated with reduced risk of falls and disability in older adults [11]. Mechanistically, the greater muscle benefits from creatine may be related to its ability to influence ATP resynthesis and PCr recovery, calcium flux from the sarcoplasmic reticulum, cell swelling, growth and myogenic transcription factors, satellite cell activity, protein kinases in the mTOR pathway, indices of protein catabolism, inflammation and oxidative stress [1,6,7,18].

In summary, the totality of research indicates that the combination of creatine supplementation and resistance training results in greater improvements in measures of lean mass, lower-limb muscle density, upper- and lower-body strength and measures of functional performance in older adults compared to resistance training alone. These results are important because an increase in muscle density and functional performance is associated with a reduced risk of falls in older adults and an increase in strength decreases the prevalence of disabilities, disease progression and premature mortality [19]. Future research is needed to determine the effects of creatine supplementation on direct measures of muscle mass in older adults.

2.2. *Creatine supplementation combined with other compounds and resistance training*

There are a few studies that have investigated the combined effects of creatine with other compounds on measures of muscle mass and performance in older adults. Whey protein has a high concentration of essential amino acids and increases the rates of muscle protein synthesis following resistance exercise [20]. Therefore, combining whey protein with creatine may further augment measures of muscle mass and performance compared to whey protein or creatine alone. However, only one study published to date has shown some benefits from combining whey protein and creatine. In healthy older males (n = 10; 59–77 yrs), the ingestion of creatine (0.1 g·kg^{-1} or ~8.3 g/day) and whey protein (0.3 g·kg^{-1} or ~25 g/day; CP) only on training days (3 days/weeks) during 10 weeks of supervised whole-body resistance training resulted in greater gains in whole-body fat-free mass (as assessed by air-displacement plethysmography) and relative upper-body maximal strength (chest press) compared to those who consumed creatine supplementation alone (C; n = 13) or placebo (PLA: n = 12) [14]. However, co-ingestion of creatine and whey protein had no effect on total-body or limb muscle thickness, lower-body maximal strength (leg press), muscle protein catabolism or measures of cytotoxicity (urinary excretion of formaldehyde; CP: 14.6 %; C: -9.1 %; PLA: 7.8 %). In healthy older males (n = 11) who underwent an intermittent creatine loading phase (7 g of creatine for 6 of 14 days) prior to supplementing with creatine (5 g/day) and whey protein (35 g/day) only on training days (3 days/week) for 14 weeks experienced similar changes in measures of muscle strength compared to older males supplementing with creatine (n = 10), protein (n = 11) or placebo (n = 10) [21,22]. Villanueva et al. [23] also found no greater effect from the co-ingestion of creatine (0.3 g/kg/day or ~24 g for 5 days followed by 0.07 g/kg/day or ~5.5 g for 79 days) and whey protein (35 g/day) during 12 weeks of resistance training on measures of lean body mass, muscle strength and endurance in healthy older males (n = 7) compared to resistance training alone (n = 7). In pre-frail and frail older females (>65 years), the combination of creatine (6 g/day) and whey protein (30 g/day) (n = 22) during 16 weeks of supervised resistance training had no effect on changes in strength, functionality or measures of kidney or liver function (alkaline phosphatase [ALP], aspartate aminotransferase [AST], alanine aminotransferase [ALT], microalbuminuria, urinary proteinuria, uric acid, ammonia) compared to whey protein (n = 22) or creatine alone (n = 22) (57). Lastly, in physically inactive older adults classified as frail, the co-ingestion of creatine (5 g/day) and whey protein (20 g/day) (n = 9) during 14 weeks of resistance training (2 days/week) resulted in similar changes in muscle mass, muscle function and measures of kidney and liver function (ALT, ALP, [AST], bilirubin, creatinine, gamma glutamyltransferase [GGT]) compared to those who consumed whey protein (n = 7) [24].

There is only one study that has examined the effects of creatine combined with CLA supplementation. There is some evidence that CLA supplementation during a resistance training program increases measures of lean tissue mass and decreases muscle protein catabolism compared to placebo [25]. Increasing lean tissue mass and decreasing muscle protein catabolism are consistent outcomes measures resulting from creatine supplementation. Therefore, the combination of CLA and creatine supplementation may lead to greater muscle benefits. Older adults ($n = 21$) who supplemented with creatine (5 g/day) and CLA (6 g/day) during 24 weeks of resistance training (2 days/week) experienced greater gains in muscle mass, strength and endurance compared to placebo (PLA) [26]. The co-ingestion of creatine and CLA (Cr-CLA) did not adversely affect measures of inflammation, oxidative stress or liver function (C-reactive protein, bilirubin, GGT, 8-isoprostanes, 8-hydroxy-2-deoxyguanosine, interleukin-6) or bone catabolism (NTx; CR-CLA males: +39.6 %; PLA males: −0.7 %; CR-CLA females: +5.6 %; PLA females: −33.4 %). Unfortunately, no comparison to creatine or CLA alone was made.

In summary, the small body of research does not suggest any additive benefits from combining creatine and whey protein in older adults. Importantly, the co-ingestion of creatine with whey protein or CLA does not pose any adverse effects on measures of kidney or liver function. Long-term studies with large sample sizes are needed to determine the mechanistic and safety effects of creatine alone, and in combination with other compounds such as whey protein and CLA, in older adults.

2.3. Creatine supplementation without resistance training

While the vast majority of research has focused on the combined effects of creatine supplementation and resistance training, a few studies have focused exclusively on creatine supplementation alone (Table 2). Gotshalk et al. published two papers in 2008 [27] and 2002 [28] from a single study involving older females ($n = 15$) and older males ($n = 10$) and showed that 7 days of creatine supplementation (0.3 g/kg/day or ~20 g/day for females, ~25 g/day for males) significantly improved whole-body fat-free mass (assessed by skinfold analyses), maximal isotonic strength (assessed by bench press and leg press 1-repetition maximum), maximal isometric strength (assessed using knee flexion/extension and left hand maximum grip test), maximal isometric upper- and lower-body mean and peak power (assessed using upper- and lower-body cycle ergometers), and measures of functionality (assessed by sit-stand and tandem gait tests) compared to those on placebo. Creatine had no effect on indices of kidney or liver function (blood urea nitrogen, ALT, AST, GGT). Using a double-blind, cross-over design, Stout et al. [29] found significant improvements in handgrip strength and cycling work capacity after 14 days of creatine supplementation (20 g/day for the first 7 days followed by 10 g/day for 7 days) in 15 older adults (7 male, 8 female) compared to placebo. Furthermore, healthy older males ($n = 10$) who supplemented with creatine (20 g/day for 10 days followed by 4 g/day for 20 days) experienced significant improvements in isokinetic lower-body muscle fatigue capacity (5 sets of 30 knee extensor muscle contractions at $180^0 \cdot s^{-1}$) after 10 and 30 days of supplementation compared to performance reductions for males on placebo ($n = 10$) [30]. Lastly, Cañete et al. [31] showed that older females (n = 10) who ingested creatine (0.3 g/kg/day or ~17 g/day; total creatine intake range: ~140 g) for 7 days experienced a significant improvement in sit-to-stand performance (measure of functionality) compared to no improvement for in females on placebo ($n = 6$). Creatine had no effect on indices of liver function (ALT, AST, GGT). Collectively, these positive findings across studies may be related to the creatine supplementation protocol implemented [32]. On average, participants consumed 20 g/day of creatine for the first 7–10 days. This strategy, often referred to as 'creatine loading', leads to significant increases in intramuscular creatine stores [33] which are associated with improvements in muscle performance in older adults [9,31].

In contrast to these studies showing some muscle benefits from creatine supplementation, Chami and Candow [35] found no greater effect from varying dosages of creatine (0.1 g/kg/day or ~8.2 g/day; 0.3 g/kg/day or ~25.4 g/day) for 10 days on measures of muscle strength (leg press, chest press and hand-grip 1-RM), endurance (leg press and chest press repetitions to volitional fatigue) or tasks of functionality (number of falls and gait speed on an elevated board) in healthy older adults ($n = 22$) compared to older adults ($n = 11$) on placebo. Furthermore, using a very low dosage creatine strategy, Lobo et al. [36] found no effect from

Table 2
Study characteristics and outcomes of research examining the influence of creatine without a resistance training program in older adults.

Study	Participant characteristics; sample size	Dosing strategy	Intervention length	Results
Baker et al. [38]	Healthy males: 54.8 ± 4.3 y, $N = 9$	CR 20 g or PLA	Acute Bolus	↔ for leg press, chest press, or RPE
Cañete et al. [31]	Healthy elderly women (age: 60–80 y); $N = 16$	CR 0.3 g/kg/d in 3 equal doses or PLA	7 d	CR ↑ sit-to-stand; ↔ 1 mile walk, VO_2max
Chami and Candow [35]	Healthy females and males (age: 58.5 ± 4.7 y); N = 33	CR-H 0.3 g/kg/d; CR-M (0.1 g/kg/d) or PLA	10 d	↔ 1RM leg press, 1RM chest press, muscular endurance leg press, muscular endurance chest press, and walking time; ↔ falls
Gotshalk et al. [28]	Healthy males (age: 59–72 y); N = 18	CR 0.3 g/kg/d in 3 equal doses or PLA	7 d	CR ↑ 1RM bench press and leg press; CR ↑ isometric knee extension and flexion; CR ↑lower body mean and peak power; ↔ on upper body power; CR ↑sit-to-stand, tandem gait, body mass and fat free mass
Gotshalk et al. [27]	Healthy females (age: 58–71 y); N = 27	CR 0.3 g/kg/d or PLA	7 d	CR ↑ bench press, leg press, body mass and fat free mass; CR ↑ time on tandem gait
Gualano et al. [55]	Vulnerable older women ≥60 y; $N = 60$	CR 20 g/day in 4 equal doses for 5 d, followed by 5 g/d for remainder	24 weeks	↔ 1RM leg press or bench press strength; ↔ on timed up and go or timed stand test; CR ↑ lean tissue mass
Lobo et al. [36]	Post-menopausal osteopenic women (age: 58 ± 6 y); $N = 109$	CR 1 g/d or PLA	1 year	↔ timed-up-and go test, timed stand test; ↔ on lean body mass, fat mass, or bone parameters.
Rawson et al. [30]	Healthy males (age: 60–82 y); N = 20	CR 20 g/d for 5 d in four equal doses followed by 4 g/d for remainder or PLA	30 d	↔ fat-free mass; ↔ isometric elbow flexor strength; CR ↑ leg fatigue performance
Sales et al. [37]	Post-menopausal women with osteopenia (age: 58 ± 6 y); $N = 200$	CR 3 g/d in 3 doses or PLA	2 years	↔ handgrip; timed-up-and-go and time stands tests. ↔ falls/fractures, LBM
Stout et al. [29]	Healthy older adults (age: 75 ± 6 y); N = 15	CR 20 g/d in 4 doses for 1 week followed by 10 g/d in 2 doses for the 2nd week or PLA. 4–6 week washout	14 d	CR ↑ handgrip and PWCFT; ↔ Sit-to-stand

CR: creatine; PLA: placebo; d: day; y: years; ↑ significant increase; ↔ no differences between creatine and placebo; UWW: underwater weighing.

creatine supplementation (1 g/day for 1 year) on measures of lean mass, muscle function (timed-up-and-go and timed-stand tests) or kidney or liver function (microalbuminuria, ALP) in postmenopausal, osteopenic females ($n = 56$) compared to placebo ($n = 53$). Increasing the daily amount of creatine to 3 g/day for 2 years resulted in no muscle benefits or adverse effects on kidney or liver function (microalbuminuria, ALP, AST, ALT) or inflammation (C-reactive protein) in the same population [37]. Finally, using a double-blind, cross-over design, Baker et al. [38] found no effect from a bolus ingestion of creatine (20 g) on leg press and chest press 1-RM strength or endurance (repetitions to volitional fatigue using 70 % baseline 1-RM) in healthy older males ($n = 9$) compared to when they consumed placebo [38]. The lack of findings across these studies may also be related to the creatine supplementation protocol used. Only one study incorporated a 'creatine loading' strategy [35] whereas the others used much lower dosages (1–8 g/day) [35–37] which were likely not high enough to produce meaningful effects over such a short period of time.

3. Creatine supplementation on aging bone, falls and fracture risk

Osteoporosis is characterized by the age-related reduction in bone mineral density and microarchitecture which can increase the risk of falls and subsequent fractures [39]. In this section we review the effects of creatine supplementation on bone, falls, and fracture risk. We have reviewed evidence from cellular studies, animal models, and human interventions.

3.1. Cellular studies

Bone cells rely on the creatine kinase reaction to generate energy from the breakdown of phosphocreatine (PCr) to resynthesize ATP [40]. Creatine kinase activity is increased when cells involved in bone formation (i.e., osteoblasts) are activated, indicating they may rely on this reaction for the resynthesis of ATP [41–43]. When creatine is added to osteoblast-like cells in culture there is stimulation of metabolic activity, differentiation, and mineralization of the cells [44]. This has provided some cellular evidence that creatine may be beneficial for bone health.

3.2. Animal models

Animal models are mixed as to whether creatine supplementation is of benefit for improving indices of bone. Four to eight weeks of creatine supplementation enhanced bone mineralization, as measured by FT-Raman spectroscopy measures of increased phosphate in trabecular bone (from the lumbar spine) in ovariectomized rats (a model of postmenopausal osteoporosis) [45] and reduced carbonate/phosphate ratio in femur of male mice [46]. Eight weeks of creatine supplementation in young growing male rats increased bone mineral density of the lumbar spine, femoral diameter, and femoral bone strength as measured directly in bending tests (i.e. bending load at failure) [47]. On the other hand, nine weeks of creatine supplementation had no effect on bone mineral density of the femur or lumbar spine in spontaneously hypertensive rats (another animal model of osteoporosis) [48]. The most comprehensive animal study involved assessment of 12 weeks of creatine supplementation during a downhill running program in ovariectomized rats [49]. Notably, this was the only animal study to assess creatine supplementation during an exercise program, with the chosen exercise (downhill running) involving substantial eccentric muscle contractions, generating high magnitude of forces, which are optimal for stimulating bone formation [50]. The exercise program was highly effective for improving bone mineral density (i.e., at the whole-body level, lumbar spine, and femur) and femoral bending strength; however, creatine supplementation had no additional beneficial effects on these measurements, nor on measures of trabecular bone architecture or osteoblast and osteoclast activity (i.e. cells involved in bone formation and resorption, respectively) [49]. Differences across studies may be due to different measurement techniques (i.e. RT-Foramen spectroscopy versus more traditional measurement techniques, such as dual energy X-ray absorptiometry for assessing bone mineral) or sex/age of the animals (i.e. young growing male rats in the study by Antolic et al. [47] versus ovariectomized female rats in the study by Murai et al. [49]).

3.3. Human studies

Stimulation of osteoblasts (i.e. cells involved in bone formation) by creatine supplementation [44] could theoretically inhibit osteoclasts (cells involved in bone resorption) because there is a linkage between the two types of cells that allows bone remodeling (i.e. bone turnover through continual activation of formation and resorption, serving to repair bone and maintain blood calcium concentrations which is important for function of excitable tissues such as muscle). Receptor activator for the nuclear factor kappa beta ligand (RANK-L) on osteoblasts binds to RANK on osteoclast precursors, which allows these precursor cells to differentiate into mature osteoclasts [51]. When osteoblasts are activated, they produce osteoprotegerin, a protein that acts as a decoy for RANK-L, which prevents RANK binding and therefore inhibits differentiation of bone-resorbing osteoclasts [51]. Short-term studies of creatine supplementation in humans can be used to assess markers of bone turnover (e.g., type I collagen break-down products in the blood or urine as a marker of resorption) before the effects on bone mineral density become evident. A number of studies indicate that creatine supplementation (~3–9 g/day) over 5–12 weeks is effective for reducing NTx in boys with muscular dystrophies (~15–18 %) [52,53], young males or females during resistance training (~30 % compared to placebo) [54] and older males during resistance training (~38 % compared to placebo) [14]. Other studies of creatine supplementation (~5 g/day) during 14–26 weeks of resistance training in older males and females however showed no effects on markers of bone resorption (NTx or CTx) [26,55] or formation (osteocalcin) [34].

Louis et al. [52] were the first to observe an increase in bone mineral density at the lumbar spine with creatine supplementation (3 g/day; 3 months) in a small group ($n = 5$) of ambulatory boys with muscular dystrophies. A beneficial effect of creatine supplementation (~7–8 g/day) during resistance training programs was confirmed in older adults, with increases in arm bone mineral content in older males (mean age 71) after 3 months [56] and femoral neck bone mineral density in postmenopausal females after 12 months [13]. Studies with lower doses of creatine (i.e., 1–3 g/d) showed no effects on bone mineral density, or trabecular architecture (as determined by high-resolution peripheral quantitative tomography) over 12–24 months [36,37], but the lower creatine doses and lack of exercise training may have been confounding factors accounting for the lack of effects. It has been proposed that exercise training may stimulate muscle creatine uptake [33] and an increase in muscle mass, which results in greater muscle forces and pull on bone to simulate bone formation. The increase in muscle mass during training programs correlates with an increase in bone mineral content [56]. Despite these promising studies, a small meta-analysis of a limited number of studies [13,26,55,57] indicated that creatine supplementation (ranging from ~5–8 g/day) during resistance training programs (3–12 months) was not effective for increasing bone mineral density as measured at the lumbar spine, femoral neck, total hip, or whole body in older males or postmenopausal females [58]. Additional studies after this meta-analysis also showed no effect of creatine supplementation (~6–8 g/d over 4–8 months) on bone mineral density at the lumbar spine or proximal femur during resistance training programs in older males or females [11,59,60]. It has been proposed that the mixed results from human studies might be due to the creatine dosage, where the majority of studies finding no effect used lower doses (i.e. 5 g/day or less) while the more effective studies used higher doses (7–9 g/d) [61]. Dose-response studies are needed to confirm this hypothesis.

Although the impact of creatine on bone mineral density, as

measured with dual-energy X-ray absorptiometry, appears equivocal across studies, creatine supplementation might have a greater impact on geometric properties of bone (e.g., bone cross-sectional area) which along with bone mineral density is a good predictor of bone strength [62]. Twelve months of creatine supplementation (~8 g/day) combined with resistance training resulted in an increase in femoral shaft subperiosteal width in postmenopausal females [13] and tended to increase ($p = 0.06$) section modulus of the femoral neck (an indicator of bone bending strength) in older males [63]. In older males and females, 12-months of creatine supplementation (~8 g/day) during resistance training increased bone area of the tibia (as measured by peripheral quantitative tomography), but with no changes at the radius and with no effects on bone density at either bone site [63]. Further randomized controlled studies are needed to confirm whether creatine indeed affects bone geometric properties to a greater extent than its effect on bone mineral density.

In addition to its impact on bone, creatine supplementation in older adults may prevent fracture by reducing risk of falling in older adults. No study has directly assessed the effect of creatine supplementation on falls in older adults, but a number of studies indicate improvements in risk factors for falls. Long-term creatine supplementation in aged mice provided neural protection and improved locomotor activity [64], which might translate into improved balance to prevent falling in humans. A recent meta-analysis indicated that creatine supplementation during resistance training programs enhances lower leg muscle strength [7,9] in older adults which theoretically could enhance lower-body stabilization to prevent falls [65]. Another meta-analysis indicated that creatine supplementation (~5 g/day for 12–24 weeks) during resistance training programs in older adults enhanced some measures of lower-leg functional performance, specifically repeat sit-to-stand testing [6] which again predicts a reduced risk of falling [66]. Other functional tests predictive of falls risks (i.e. timed up and go) however were not enhanced with creatine supplementation [60]. Finally, an assessment of muscle quality (i.e., muscle density) of the lower leg was enhanced with creatine supplementation (~8 g/day for 12 months) in older males and females [63]. This muscular assessment is a good predictor of falls risk [67]. Further research is needed to determine whether long-term supplementation with creatine in older adults actually reduces direct measures of falls.

4. Creatine supplementation and frailty

Frailty is overarchingly described as a condition of musculoskeletal weakness and reduced function. Though several definitions and screening criteria exist, frailty has generally been used to broadly define older adults impacted by weight loss, functional deficits, fatigue, cognitive impairment or mood disorders, comorbidities and poor nutritional status [68]. Ultimately, frailty is considered to be state of increased vulnerability (particularly to adverse health outcomes) that is associated with an increased risk of falls, disabilities, lack of independent living and mortality [69,70]. Recognized as an aging condition, recent estimates suggest that approximately 1 in 6 community dwelling older adults can be characterized as frail [71]. Others have identified the prevalence of frailty up to ~59 % in older populations [72]. Consequently, the alarming incidence of frailty in older adults underscores the importance of maintaining and/or increasing muscle mass, strength and physical function in individuals with frailty to preserve health-related quality of life.

Exercise is routinely recommended as a therapeutic aid in the management of pre-frail and frail conditions [73]. A recent umbrella review indicated that resistance training could significantly increase muscular strength, gait speed and physical function in community dwelling pre-frail and frail older adults (≥60 years) [74]. As previously discussed, creatine supplementation has been consistently demonstrated to augment resistance training adaptations, yielding improvements in lean mass, muscle strength and physical function, relative to resistance training alone in healthy older adults [7–9]. However, evidence from randomized controlled trials of creatine supplementation specifically in pre-frailty and frail conditions remains scare [1]. Collins et al. [24] demonstrated that individuals supplementing with creatine (5 g/day) during 12-weeks of resistance training experienced improvements in physical function (handgrip strength, timed up and go, and timed sit-stands) [24]. In a multi-factorial, double-blind randomized controlled trial, Roschel et al. [60] found no additional improvements in muscle strength and lean mass with creatine supplementation, relative to those achieved with resistance training alone. These findings of no additional benefit of creatine supplementation could be due to low sample size, length of interventions, or that individuals with pre-frailty or frailty are resistant to dietary interventions to augment resistance training. However, the consistent and reliable improvements in muscle accretion and strength demonstrated in healthy older adults from creatine supplementation indicate strong potential for the application of creatine as a therapeutic intervention for individuals with pre-frailty or frailty. Further, creatine supplementation may improve certain domains of cognitive function (i.e. memory and reasoning) [32,75–77] and has been demonstrated to have neuroprotective effects and anti-inflammatory properties in preclinical studies [78,79]. Consequently, the therapeutic benefits of creatine supplementation in frailty could extend beyond physical function, to address the multifactorial components of a frail condition. Future large scale randomized controlled trials designed to specifically test the effects of creatine supplementation in individuals with pre-frailty of frailty are warranted to better understand the potential application of creatine in these individuals.

5. Creatine supplementation and Cachexia

Cachexia is used to define a complex, multifactorial, and often aggressive muscle wasting condition, characterized by progressive weight loss (with or without fat loss), that cannot be reversed with conventional nutritional support [80,81]. Cachexia is strongly associated with poorer prognosis, worsening of physical function and quality of life (QOL), and reduced survival in a variety of populations, such as cancer, chronic kidney disease and heart failure [82–85]. Cachexia can arise due to a combination of factors, including systemic inflammation, reduced protein synthesis and/or an increase in catabolism, along with malnutrition and physical inactivity [86–89].

The use of creatine as a therapeutic aid in the management of cachexia is largely underdeveloped. Several trials have investigated creatine supplementation alone vs. placebo in adults and/or children with cancer [90–92], with relatively no effect on outcome measures of muscle mass and strength. However, these studies all used creatine supplementation in isolation (i.e., without an exercise intervention). As outlined earlier, the ergogenic benefits of creatine supplementation largely stem from an increase in intramuscular PCr, increasing the rephosphorylation of adenosine diphosphate to adenosine triphosphate during exercise [93]. Subsequently, creatine supplementation should enhance exercise training capacity, which over time could augment adaptations in muscle mass, strength, and perhaps functionality. Further, considering cachexia is a multifactorial syndrome, it's strongly suggested that a multimodal approach is needed to adequately target the reversal of muscle wasting [81,82,88,94,95]. Lønbro et al. [96] examined the effects of creatine supplementation in combination with protein and resistance training on muscle strength and physical function in individuals with head and neck cancer patients that received radiotherapy [96]. Results showed that the combination of creatine, protein and training increased lean mass by 2.6 kg compared to a 1.3 kg increase for resistance training alone. Individuals with head and neck can often experience notoriously large losses in body weight and lean mass. Consequently, an additional ~1 kg of lean mass experienced by individuals receiving protein and creatine could be considered clinically significant and worth further inquiry. However, the authors urged caution in interpretation of the results due to the low number of

participants, minimal supervision during the training sessions, and adherence to the supplement only being reported using a questionnaire.

Several trials are ongoing, investigating the impact of creatine supplementation in individuals with cancer [97–99]. Though not directly in cachexia, these results will inform of the potential application of creatine supplementation in clinical populations burdened by low muscle mass and function. Irrespective, the loss of body weight and muscle, along with reduced physical function experienced by individuals with cachexia represent clinically relevant outcomes that creatine supplementation could potentially target in conjunction with resistance training.

6. Conclusions

The current body of research indicates that creatine monohydrate supplementation, primarily when combined with resistance training, is a viable lifestyle intervention to improve aging muscle mass, strength and measures of functionality, which may decrease the risk of falls and fractures in older adults. The combination of creatine and resistance training has some beneficial effects on aging bone. However, these benefits disappear when no exercise intervention is used. Despite having some musculoskeletal benefits, the effects of creatine supplementation in individuals diagnosed with sarcopenia, osteoporosis, frailty and cachexia is relatively unknown. Long-term, large scale RCT's are needed to determine the efficacy of creatine supplementation, with and without resistance training, in these clinical populations.

CRediT authorship contribution statement

Conceptualization, D.G.C.; writing—original draft preparation: all authors; writing—review and editing: all authors. All authors have read and agreed to the revised version of the manuscript.

Declaration of competing interest

DGC, BG, and HR have conducted industry sponsored research involving creatine supplementation and received creatine donations for scientific studies and travel support for presentations involving creatine supplementation at scientific conferences. DGC serves as an expert witness/consultant in legal cases involving creatine supplementation. In addition, DGC and BG serve on the Scientific Advisory Board for Alzchem (a company that manufactures creatine). SCF has served as a scientific advisor for a company that sells creatine products. All other authors declare no conflicts of interest.

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