A High Dose of Creatine Combined with Resistance Training Appears to Be Required to Augment Indices of Bone Health in Older Adults

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Dear Editor,

Creatine is a ubiquitous nitrogen-containing molecule that can be synthesized endogenously in the liver, kidneys, and pancreas or exogenously ingested from foods (e.g., red meat, seafood, and poultry) or ingested as a dietary supplement. Creatine supplementation is purported to enhance the aging bone [1]. Creatine may impact the bone via indirect and direct mechanisms [1]. Indirectly, creatine supplementation elevates phosphocreatine stores in skeletal muscle, increasing the capacity to re-synthesize adenosine triphosphate leading to a greater resistance training capacity and augmenting gains in muscle mass and strength over time [2]. Greater muscle mass and strength results in enhanced muscle pull and stress on the bone during resistance exercise leading to bone accretion. Creatine may also have a direct impact on the bone. Osteocytes rely on phosphocreatine breakdown via creatine kinase reactions [3]. Furthermore, in a low serum cell culture medium, the addition of creatine increases the metabolic activity and differentiation of osteoblast cells (cells involved in bone formation) [4]. Stimulating osteoblast cell activity elevates osteoprotegerin production, a protein that inhibits osteoclast cell activity

and decreases bone resorption [1]. In young healthy males and females, creatine (9 g/day for 5 weeks) decreased urinary excretion of cross-linked n-telopeptides of type I collagen (a marker of bone resorption) by 3.6% compared to a 26% increase in conjunction with an intense resistance training regime [5]. In aging males, creatine supplementation (8 g/day for 10–12 weeks) combined with resistance training decreased bone resorption [6].

Currently, there are 10 human randomized placebo-controlled trials investigating creatine combined with resistance training on indices of bone health (summarized in Table 1). Results across individual studies are mixed with some studies showing a positive effect, while others found no effect. Upon closer examination of individual studies, the dose of creatine appears to be an important determinant altering the efficacy of creatine on indices of bone health. Four studies used a dose of 5 g/day of creatine with and without a loading phase (Table 1). All 4 studies were unable to enhance any markers of bone health. The remaining 6 studies used a higher relative dose of creatine (0.1 g/kg/day; ~7–9 g/day); of these studies, 5 out of 6 found at least 1 positive outcome on bone

Table 1. Study characteristics and outcomes of research examining the influence of creatine with a resistance training program on the bone

First author	Study population	Intervention	Duration	Outcomes
Brose et al. [11]	N = 28; healthy (15 men, 13 women); age: men = 68.7 yr, women = 70.8 yr	RCT; CR + RT, PLA + RT. Creatine was provided 5 g/day. RT = 3x/wk	14 wk	↔ on osteocalcin
Candow et al. [6]	N = 35; older men (age: 59–77 yr)	RCT; CR + PRO + RT; CR + RT, PLA + RT; creatine was provided 0.1 g/kg/day; RT = 3x/wk	10 wk	CR↓NTx
Candow et al. [12]	N = 39; healthy (17 men; 22 women); age ≥50 yr (mean ~55 yr)	RCT; CR-before + RT, CR-after + RT, PLA + RT. Creatine was provided 0.1 g/kg/day. RT = 3x/wk	8 mo	↔ BMD and BMC of the whole-body, limbs, femoral neck, lumbar spine, and total hip
Candow et al. [13]	N = 38; healthy men; age = 49–67 yr	RCT; CR + RT, PLA + RT. Creatine was provided 0.1 g/kg/day. RT = 3x/wk	12 mo	↔ BMD and geometry; bone speed of sound. CR ↑ ($p = 0.06$) section modulus of the narrow part of the femoral neck
Forbes et al. [9]	N = 70; healthy men and women; age = 58±6 yr	RCT; CR + RT, PLA + RT. Creatine was provided 0.1 g/kg/day. RT = 3x/wk	12 mo	↑ total bone area in the distal tibia and tibial shaft. ↑ trabecular and cortical bone area in the tibia for men. ↑ lower leg muscle density
Chilibeck et al. [14]	N = 29; older men (71 yr)	RCT; CR + RT, PLA + RT. Creatine was provided 0.3 g/kg/day for 5 days and then 0.1 g/kg/day for the remaining. RT was performed 3x/wk	12 wk	↑ arm BMC greater in the CR group compared to PLA. ↔ between groups for whole-body and leg BMD (sig. Main effect for time)
Chilibeck et al. [15]	N = 33; postmenopausal women; age: 57±6 yr	RCT: PLA + RT or CR + RT. Creatine group received 0.1 g/kg/day (0.05 g/kg provided immediately before and 0.05 g/kg after training on training days and with 2 meals on nontraining days). PLA received corn starch maltodextrin. RT was performed 3x/wk	12 mo	CR attenuated rate of femoral neck BMD loss compared to PLA and ↑ femoral shaft subperiosteal width. CR ↑ bench press strength more than PLA. ↔ between groups on all other outcome measures
Gualano et al. [16]	N = 60; older vulnerable women (age: 66 yr)	RCT: PLA, CR, PLA + RT, CR + RT. Creatine was provided 20 g/day for 5 days followed by 5 g/day for the remaining 24 wk. RT = 2x/wk	24 wk	CR + RT ↑ appendicular lean mass accrual compared to all other groups. ↔ fat mass, bone mass, and serum bone markers between groups
Pinto et al. [17]	N = 32; healthy, nonathletic men and women between 60 and 80 yr	RCT: PLA + RT or CR + RT. Creatine group received 5 g/day. PLA received 5g/day of maltodextrin. RT was performed 3x/wk for 60 min and progressed on an individual basis. Muscle groups (i.e., upper and lower body) alternated between training days; 1.5x/week per muscle group	12 wk	CR + RT ↑ lean mass compared to PLA + RT. ↔ 10 RM in bench press or leg press, body composition, BMD, and BMC of all assessed sites between groups
Tarnopolsky et al. [18]	N = 39; older men and women (65–85 yr)	RCT; CR + CLA + RT, PLA + RT. Creatine was provided 5 g/day. RT = 2x/wk	6 mo	↔ between groups for total BMD, hip, and lumbar BMD

RCT, randomized controlled trial; PLA, placebo; RT, resistance training; CR, creatine; RM, repetition maximum; BMD, bone mineral density; BMC, bone mineral content; ↑, significantly greater; ↔, no difference between conditions; wk, weeks; yr, years; g, grams; kg, kilograms.

health. It is well established that 5 g/day of creatine is sufficient to saturate skeletal muscle [7]; however, recent evidence suggests that a higher dose may be superior to augment resistance training strength adaptations (particularly in lower body strength) in older adults [8]. Future research is urgently needed to examine a dose-response relationship of creatine supplementation combined with resistance training on whole body, regional changes, and potential mechanisms to confirm these findings. It is also important to note that creatine must be combined with resistance training to alter bone, reviewed by Forbes et al. [9]. For example, Sales et al. [10] conducted a large 2-year longitudinal trial with creatine (3 g/day) without an exercise intervention and found no effect on bone.

In conclusion, a high dose of creatine combined with resistance training appears to be an effective strategy to enhance bone. A lower dose of 5 g/day is not sufficient to augment indices of bone health.

Statement of Ethics

An ethics statement was not required for this study type, as no human or animal subjects or materials were used.

Conflict of Interest Statement

S.M.O. serves as a member of the Scientific Advisory Board on creatine in health and medicine (AlzChem LLC, Trostberg, Germany). S.M.O. owns patent “Sports Supplements Based on Liquid Creatine” at European Patent Office (WO2019150323 A1) and active patent application “Synergistic Creatine” at UK Intellectual Property Office (GB2012773.4). S.M.O. has served as a speaker at Abbott Nutrition, Chicago, IL, USA, a consultant of Allied Beverages Adriatic and IMLEK, and an advisory board member for the

University of Novi Sad School of Medicine and has received research funding related to creatine from the Serbian Ministry of Education, Science, and Technological Development, Provincial Secretariat for Higher Education and Scientific Research, AlzChem GmbH, Trostberg, Germany, KW Pfannenschmidt GmbH, Hamburg, Germany, ThermoLife International LLC, Phoenix, AZ, USA, and Monster Energy Co., Corona, CA, USA. S.M.O. does not own stocks and shares in any organization. S.C.F. has previously served as a scientific advisor for a company that sold creatine. D.G.C. has 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. In addition, D.G.C. serves on the Scientific Advisory Board for AlzChem (a company that manufactures creatine). The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

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Author Contributions

The authors' responsibilities were as follows: S.C.F. and D.C.G. designed and wrote the draft of the manuscript and has primary responsibility for the final content, and all authors read and approved the final version of the manuscript.

Data Availability Statement

Data described in the manuscript will be made available upon request.

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