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The Role of Creatine in Enhancing Bone Health Among Postmenopausal Women

1. Michał Szczepański [MS]

Jędrzej Śniadecki Regional Hospital in Białystok, Marii Skłodowskiej-Curie 26 Street, 15-278 Białystok, Poland

https://orcid.org/0009-0002-4828-6709

michalszczepanski99@gmail.com

2. Natalia Dzieszko [ND]

Jędrzej Śniadecki Regional Hospital in Białystok, Marii Skłodowskiej-Curie 26 Street, 15-278 Białystok, Poland

https://orcid.org/0009-0008-8743-6590

1nataliadzieszko9@gmail.com

3. Maciej Borowski [MB]

Univeristy Clinical Hospital of Bialystok, Marii Skłodowskiej-Curie 24A street, 15-276 Białystok, Poland

https://orcid.org/0009-0006-4185-2199

mborowski800@gmail.com

4. Anna Ewelina Francuziak [AEF]

University Hospital in Krakow, Kopernika 36 street, 31-501 Krakow, Poland

https://orcid.org/0009-0005-9810-7758

anna.fr17@wp.pl

5. Piotr Mikołaj Dembicki [PMD]

Ludwik Rydygier Memorial Specialized Hospital, Osiedle Złotej Jesieni 1 street, 31-820 Krakow, Poland

https://orcid.org/0009-0005-0709-9220

piotr.dembickizmc@gmail.com

6. Kinga Kozłowska [KK]
Provincial Hospital of Podkarpackie John Paul II in Krosno, Korczyńska 57 street, 38-400 Krosno, Poland
https://orcid.org/0009-0008-6541-207X
Kinga7839@gmail.com
7. Tomasz Karol Książek [TKK]
Univeristy Clinical Hospital of Bialystok, Marii Skłodowskiej-Curie 24A street, 15-276 Białystok, Poland
https://orcid.org/0009-0000-9852-1434
ksitomasz@gmail.com
8. Aleksandra Szeliga [AS]
Medical Univeristy of Białystok, Jana Kliniśkiego 1 street, 15-089 Białystok, Poland
https://orcid.org/0009-0006-1832-5569
Aleksandra.sze97@gmail.com
9. Weronika Kalinowska [WK]
Jędrzej Śniadecki Regional Hospital in Białystok, Marii Skłodowskiej-Curie 26 Street, 15-278 Białystok, Poland
https://orcid.org/0009-0005-4630-467X
wkalinowska999@gmail.com
10. Paulina Sara Kulasza [PSK]
Jędrzej Śniadecki Regional Hospital in Białystok, Marii Skłodowskiej-Curie 26 Street, 15-278 Białystok, Poland
https://orcid.org/0009-0003-5829-6721
pkulasza@onet.pl

Abstract

Given the high popularity of creatine as a dietary supplement, its pleiotropic effects, and its well-established safety profile, it is worth considering as an adjunct therapy for osteoporosis—a condition that predominantly affects postmenopausal women due to hormonal changes, particularly a decline in estrogen levels—and has become a silent epidemic of the 21st century. Creatine may indirectly enhance muscle mass and strength, leading to increased mechanical stress on bones, and some studies suggest that creatine might also directly influence osteoblast

activity and bone metabolism, potentially promoting bone formation. These direct and indirect mechanisms may improve bone health in at-risk women, reducing the risk of falls and fractures and ultimately contributing to a better quality of life. This research explores the effects of creatine on bone remodeling, metabolic activity, resistance training performance, and its potential anti-inflammatory properties in the context of skeletal health maintenance. It also examines appropriate creatine dosing in older adults—which typically does not require a loading phase—and evaluates the safety of creatine use in aging women.

Material and methods

Databases such as Pubmed and GoogleScholar were used for research with the key words: osteoporosis, creatine, creatine supplementation, bone health, postmenopausal women, resistance training.

Conclusions

The results of studies on the effects of creatine supplementation on bone health among postmenopausal women are unclear and require further research. Some of them indicate a synergistic, positive effect of creatine supplementation combined with resistance training, which gives hope for its use in osteoporosis- supportive therapy. Taking part in multiple metabolic pathways, creatine may also exhibit anti-catabolic and anti-inflammatory effects and influence bone metabolism.

Key words: osteoporosis, creatine, creatine supplementation, bone health, postmenopausal women,

1. Introduction

Osteoporosis is a systemic condition affecting the skeletal system, characterized by reduced bone mass and the degradation of bone microarchitecture.[1] It is particularly common among

postmenopausal women, who face an increased risk of fractures due to a decline in estrogen levels and ongoing bone loss—factors associated with significant morbidity and mortality. Additional major risk factors for postmenopausal osteoporosis include advanced age, genetic predisposition, smoking, low body weight, and various medical conditions or medications that negatively impact bone health.[2]

Addressing modifiable risk factors, along with implementing exercise and supplementation of calcium and vitamin D, plays a crucial role in supporting the pharmacological treatment of osteoporosis. Medication options include bisphosphonates, hormone replacement therapy (HRT), selective estrogen receptor modulators (SERMs), calcitonin, parathyroid hormone (PTH)[3], denosumab and romosozumab.[4]

The existing body of research examining the impact of creatine supplementation in women indicates that the risk-to-benefit ratio is minimal. [5] Additionally, research shows that creatine monohydrate supplementation, especially when paired with resistance training, positively impacts markers of aging in muscle and bone.[6]

This study seeks to clarify the role of creatine supplementation in enhancing bone health in postmenopausal women.

2. Osteoporosis epidemiology

Osteoporosis is a serious and advancing condition that remains unnoticed until symptoms arise and is recognized as the most prevalent metabolic bone disorder. This illness has been referred as "the quiet epidemic of the 21st century" due to its implications for public health.[7] Nearly 10% of the global population and 30% of postmenopausal women are affected by osteoporosis.[8] Epidemiological research estimates that 200 million women suffer from osteoporosis - approximately one in ten women aged 60, one in five of women aged 70, two in five of women aged 80 and two out of three women aged 90.[9] The International Osteoporosis Foundation has indicated a tendency among postmenopausal women to deny personal risk, a lack of discussion about osteoporosis with their physicians and limited access to diagnosis and treatment before the initial fracture, leading to under-diagnosis and undertreatment of the condition.[10]

3. Creatine: Overview

Creatine (methylguanidine-acetic acid) is produced naturally through reactions that involve the amino acids arginine, glycine, and methionine in the liver, kidneys [11] and pancreas.[12] More specifically, the kidneys carry out the first stage of synthesis to form guanidinoacetic acid from arginine and glycine. Guanidinoacetic acid is then transported to the liver, which is responsible for converting it to creatine with the involvement of the methyl donor S-adenosyl-methionine. [13] Endogenous synthesis of creatine meets approximately 50% of the daily requirement for creatine.[14] Exogenous creatine is mainly obtained from meat and/or taken as a dietary supplement. [11] Creatine breaks down into creatinine, which is eliminated in the urine at an approximate rate of 2 g/d. Approximately 90–95% of the body's creatine is located in skeletal muscle. Of this, about one-third is unbound creatine, while two-thirds are present as phosphocreatine (PCr). The absorption from circulation is an active process enabled by a Na+-dependent transporter working against a concentration gradient [12], encoded by the SLC6A8 gene.[15] PCr plays a significant part in energy metabolism. As energy requirements rise, PCr donates its phosphate to ADP to create ATP. The ATP-PCr system can deliver energy quickly, but only for a brief period before the PCr supply is depleted.[12] Supplementing with creatine boosts intramuscular creatine reserves, potentially leading to elevated PCr levels. [16] In general, creatine (especially when used alongside resistance training) has demonstrated an enhancement in muscle growth, strength, and functionality. Creatine also been shown showed to enhance bone area and strength, slow down the rate of bone mineral loss, and affect bone turnover by decreasing the urinary excretion of cross-linked N-telopeptides (NTx) or C-telopeptides of type I collagen (CTx) in older individuals. Evaluating bone turnover markers (i.e., NTx, CTx) is clinically significant because they offer crucial insights into the bone remodeling process and forecast the likelihood of osteoporotic fractures in older individuals.[6]

4. Mechanisms by Which Creatine May Enhance Bone Health

1. Creatine supplementation without training

Two randomized controlled studies have examined the impact of creatine supplementation (without resistance training) on the structural properties of cortical and trabecular bone in older adults and revealed no effects from creatine supplementation (1 g/d for

1 year) in comparison to placebo in bone mineral density at femoral neck, lumbar spine, total femur and whole body of postmenopausal women.[17] An important disadvantage of this study was usage of low creatine dose, which could be the reason for such test results, but an increased dosage and therapy length of creatine (3 g/d for 2 years) similarly showed no effect in postmenopausal women. In this study microarchitecture, bone markers and the count of falls/fractures remained unaffected by creatine.[18,19]

4.2 Influence of resistance training

Exercise training, especially resistance training, is essential for preserving musculoskeletal health in an aging population. It exerts mechanical stress on the bones, leading to their strengthening. [20] However, inactivity or extended periods of bed rest quickly results in hypercalciuria, a negative calcium balance, and loss of bone density.[21]

One study focused on older adults (mostly over 50 years old) investigated the creatine supplementation impact on changes in muscle strength. This study showed that after 10 weeks of resistance training (lasting 70 minutes, including 10 minutes each of warm-up and cool-down) and creatine supplementation (0.1 g/kg of body weight), the average increase in muscle strength (average of the seven muscle groups tested) in the placebo-treated group was 35.9%, and 57% in the creatine-treated group. These results indicate a synergistic effect of creatine supplementation with resistance training.[22] Findings from another study conducted in which creatine was supplemented and resistance training was performed for 24 weeks also suggest that creatine supplementation improved muscle function.[23]

Enhanced muscle strength and mass due to Cr supplementation might elevate stress on bone, which over a period could encourage bone growth. [18,24]

Moreover, physical activity significantly impacts hormones by controlling estrogen, PTH, and glucocorticoid levels, which play a role in bone metabolism.[25]

1. Effect of creatine on the effectiveness of resistance training and bone remodeling

Research indicates that creatine supplementation paired with resistance training demonstrates greater efficacy in workouts and enhanced muscle strength. [26,27] Moreover, one of the randomized controlled trials examined the joint impacts of creatine supplementation (0.1 g/kg of body weight) and one year, monitored whole-body resistance training on bone architecture

and revealed that supplementation with creatine enhanced the overall bone area in the distal tibia and the shaft of the tibia.[18]

Regrettably, findings from the recent meta-analysis and studies presented afterward indicated no significant impact of creatine supplementation on bone mineral density in the total hip, femoral neck, lumbar spine, or overall body. [28,29] It is important to recognize that bone remodeling occurs slowly, so extended interventions are more likely to yield positive results. [30]

The most successful intervention demonstrated that creatine supplementation (~8 g/day) for 12 months, alongside resistance training (three times weekly), in postmenopausal women reduced the decline of bone mineral density at the femoral neck compared to placebo (i.e., a loss of 1.2% in the creatine group versus 3.9% in the placebo group).[31] This research also indicated that geometric characteristics at the femur (i.e., the subperiosteal width of the femoral shaft) were heightened with creatine supplementation which could enhance the bending strength of bone. This study faced limitations due to a relatively small sample size and the notably high bone mineral density loss in the placebo group, raising the likelihood that the results were coincidental.[32]

So there are still some reports that creatine combined with moderate to high-intensity exercise in older adults may enhance skeletal muscle health.[16,33] As I mentioned before, a proposed mechanism through which creatine could benefit bone is the heightened strain on bone resulting from an increased muscle mass (and consequently strength) during muscle contractions. [34]

Worth mentioning, is that the study involving people with type 2 diabetes showed that creatine supplementation during 12 weeks of resistance training increased the amount of glucose transport protein 4 in the cell membranes of muscle fibers.[35] That could improve glucose absorption in muscle to promote glycogen storage. This topic requires further research, but may result in better adaptation to resistance training.[16]

4.4 Effect of creatine on bone metabolic activity

One of the studies indicated that Cr had distinct stimulatory effects on metabolic activity, differentiation of primary rat osteoblast-like cells, and the mineral deposition by these cells. Therefore, Cr supplementation may potentially serve as an additional treatment for bone fracture healing or be included in an osteoporosis treatment plan. [36] Unfortunately, although

creatine supplementation shows potential benefits, further research assessing 5 g/day of creatine for 14–26 weeks in older adults undergoing resistance training has not found any effects on blood or urine indicators of bone formation or resorption. [32]

4.5 Impact on osteoprotegerin

Another study highlighted that in vitro creatine supplementation might improve osteoblast activity, leading to an increased synthesis of collagen type I and osteoprotegerin (OPG). The studied tissues were collected from healthy and osteopenic subjects. [37] OPG serves as a decoy receptor for RANKL, a key factor in the differentiation and activation of osteoclasts. By increasing OPG levels, creatine indirectly inhibits osteoclastogenesis, potentially resulting in reduced bone resorption. [38]

4.6 Anti-inflammatory and anti-catabolic effect

Moreover, human aging is linked to increased low-grade inflammation, which adversely impacts skeletal muscle and bone. [39] Evidence from diverse research groups shows that creatine supplementation can offer anti-inflammatory and anti-catabolic benefits. These results might be useful for older individuals at risk of losing muscle and bone.[39] Creatine supplementation helps prevent oxidative stress and inflammation and may offer protection against tissue and mitochondrial DNA damage. Aging-related mitochondrial defects can result in elevated generation of reactive oxygen species, causing inflammation and muscle wasting.[16] The first reports of creatine's antioxidant properties came from an in vitro study in which creatine was shown to have the capability to eliminate the superoxide anion radical, ABTS+ cation, and peroxynitrite radical (ONOO-).[40] Further study involving seven days of creatine supplementation, measuring malondialdehyde (MDA), which is indicative of lipid peroxidation, in plasma and 8-hydroxy-2-deoxyguanosine (8-OHdG), which is indicative of DNA oxidation, in urine (before and after the seventh day of supplementation) before, immediately and 24 hours after a unit of resistance training, showed a mean decrease in the concentration of these compounds compared to the placebo group, indicating creatine's ability to reduce oxidative DNA damage and lipid peroxidation.[41]

The results of studies on the anticatabolic properties of creatine in relation to muscle are unclear. There are reports of positive effects of supplementation on muscle tissue degradation. Studies using measurements of urinary 3-methylhistidine (3-MH) in urine or the leucine infusion technique have proven decreased rates of muscle protein catabolism in creatine-supplemented subjects relative to the placebo group.[39,42,43,44,45,46] However, a systematic review and meta-analysis involving 278 participants contradicts these results, suggesting that creatine supplementation lowered the levels of leucine oxidation and protein degradation, which are indicators of muscle damage caused by exercise, only in men, with no such benefit observed in women.[39,47]

In addition to creatine's anti-catabolic benefits for muscle, some evidence suggests that creatine supplementation during resistance training may reduce rates of bone catabolism, potentially affecting the bone remodeling process. Older men who supplemented with creatine at a dose of 0.1g per kilogram of body weight per day, or 9g/d, and performed resistance training for 10 weeks at a frequency of three workouts per week achieved significant reductions (more than twofold) in cross-linked N-telopeptides of type I collagen, a marker of bone turnover.[39,46] On the other hand, in a study involving older females, lasting 24 weeks, with creatine supplementation (a loading dose of 20g/d for 5 days and a maintenance dose of 5g/d) and including whole-body resistance training, it was found that serum bone markers did not show significant differences between the study groups.[48]

4.7 The role of creatine in the prevention of falls and bone fractures

Due to weakened bone structure, decreased muscle mass, and reduced motor coordination, resulting in impaired ability to maintain balance, older people are at risk of more frequent falls.[49] Moreover, osteoporosis makes a person more susceptible to fractures in various skeletal areas. [50] A meta-analysis that included studies of older males and females who were randomly assigned to receive either creatine or a placebo while engaging in resistance training revealed that creatine supplementation leads to a notable enhancement in sit-to-stand performance when compared to the placebo group. [26]

5. Safety and Potential Risks

Studies and meta-analyses conducted to date using creatine in the elderly have not shown any negative effects of creatine supplementation on the kidneys or liver.[16] In a study involving postmenopausal women, creatine supplementation (0.1 g/kg/day) over the course of 1 year showed no impact on markers of liver (bilirubin, alanine aminotransferase, aspartate aminotransferase and alkaline phosphatase) or kidney (urea, albumin, urine protein, and creatinine clearance) function. [31] Another study with creatine dosage 1g/d for 1 year supplementation also revealed that it was free of adverse effects for older women. [17] The metabolic breakdown of creatine generates formaldehyde, which may be cytotoxic. However, findings from a study indicate that low-dose creatine supplementation (around 8 g·d−1) on training days among older men did not elevate formaldehyde production, measured by urinary formaldehyde levels. There were no differences observed between the creatine and placebo groups.[46] Moreover, the existing evidence does not suggest that creatine supplementation raises total testosterone, free testosterone, DHT, or leads to hair loss/baldness. [11] Additionally, a recent position paper from the International Society of Sports Nutrition determines that creatine supplementation poses no negative effects for older adults.[51,52] However, in order to be certain of the absence of adverse effects of creatine supplementation, a larger number of people than has been studied so far, measuring about 700 adults, is necessary.[13,16] It is also important to consider that commercially available creatine products do not have control standards like drugs and may contain unwanted contaminants in them or the dose consumed may differ from that on the manufacturer's label.[12]

6. Dosage

Several supplementation strategies have been proposed to effectively enhance muscle levels of creatine. The amount of increase in muscle creatine concentration before and after the inclusion of creatine supplementation depends on its baseline level and is correlated to the training efficiency. Therefore, people with a small amount of stored creatine, such as vegetarians who do not consume meat products are predisposed to an increase in muscle creatine stores of about 20-40%, when those with a larger store experience only 10-20%. [52] One of the recommended dosage of creatine supplements includes a loading phase of 20 grams of creatine monohydrate for 4-6 days, frequently split into smaller dosages followed by a maintenance phase of about 2 grams for 2-3 weeks. This amount of creatine intake should theoretically ensure its optimal

concentration for muscle uptake. Any higher doses taken would result in the excretion of excess creatine through the kidneys. It is possible to supplement with creatine at a lower dose measuring 2-3 grams per day, however, this is associated with a much slower increase in creatine concentration in the muscles.[12] It is also possible to dose creatine supplements based on body weight, which is equal to 0.03g per kilogram of body weight per day during loading phase. [53] Other available creatine supplementation protocols include dosages 3-6g per day [52] or 0.1g per kilogram of body weight per day[11], or "cycling" protocols involving taking a loading dose for 3-5 days every 3-4 weeks to prevent creatine concentrations from returning to baseline.[52] Worth noting that, creatine loading strategies find use mainly among athletes needing to maximize the ergogenic potential of creatine supplementation very quickly.[11]

Conclusions

Creatine exhibits pleiotropic effects, including anti-inflammatory properties, modulation of resistance training outcomes, and influence on bone metabolic activity. However, research findings regarding the impact of creatine supplementation on bone health in postmenopausal women remain inconclusive. Some studies suggest that creatine supplementation, when combined with resistance training, may have a synergistic effect on bone mineral properties, geometry, and microarchitecture, offering potential as a supportive therapy for osteoporosis. Nevertheless, further research is necessary—particularly involving larger sample sizes and longer intervention periods—given the relatively slow rate of bone remodeling. The influence of creatine on bone metabolic function warrants particular attention, as creatine plays a role in numerous metabolic pathways.

Author contribution

Conceptualization: Michał Szczepański, Natalia Dzieszko, Maciej Borowski
Methodology: Michał Szczepański, Natalia Dzieszko
Investigation: Michał Szczepański, Natalia Dzieszko, Tomasz Karol Książek
Software: Piotr Mikołaj Dembicki, Anna Ewelina Francuziak, Kinga Kozłowska, Tomasz Karol Książek
Check: Anna Ewelina Francuziak, Kinga Kozłowska

Data curation: Kinga Kozłowska, Piotr Mikołaj Dembicki

Visualization: Anna Ewelina Francuziak, Piotr Mikołaj Dembicki

Project administration: Michał Szczepański

Writing -rough preparation: Michał Szczepański, Natalia Dzieszko

Formal analysis: Piotr Mikołaj Dembicki, Anna Ewelina Francuziak, Aleksandra Szeliga

Writing –review and editing: Piotr Mikołaj Dembicki, Aleksandra Szeliga

Resources: Maciej Borowski, Paulina Sara Kulasza, Weronika Kalinowska

Supervision: Maciej Borowski, Paulina Sara Kulasza, Weronika Kalinowska

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