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Creatine supplementation: facts and myths

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Abstract

Introduction: Creatine (N-methylguanidinoacetic acid) is a peptide built of three amino acids: glycine, arginine and methionine. Its function is to store energy. It is common practice to intake creatine as a dietary supplement. Because of that, we decided to try to answer the question if there are scientifically documented advantages of creatine supplementation.

Review method: We analyzed the newest research conducted from 2017 to 2024. The studies were searched in online databases like PubMed and Google Scholar. We focused on the impact of creatine supplementation on the ageing population, professional athletes, the course of some diseases, cognitive functions and body composition

Results: Creatine supplementation is beneficial in professional sports. There are some signals that creatine may worsen lung conditions in sportsmen. In the ageing population, creatine supplementation boosts the results of resistance training on ageing muscle performance. There are suggestions that in this population bone geometry changes due to a combination of training and creatine supplementation may be protective against hip fracture. Creatine can also enhance cognitive functions as well as lead to positive changes in body composition. Supplementation of creatine seems to reduce symptoms of long COVID-19. It may be also beneficial among children with dermatomyositis and patients with ischemic heart disease.

Conclusions: Creatine supplementation may be beneficial in some populations. It can also enhance cognitive functions as well as lead to changes in body composition. Some effects of creatine supplementation are still controversial and further investigation is needed to determine its usefulness.

Keywords: creatine, body composition, long COVID-19, ageing population, professional sport, cognitive functions, dermatomyositis, ischemic heart disease

Introduction

Creatine (N-methylguanidinoacetic acid) is an oligopeptide built of three amino acids: glycine, arginine and methionine. In human organisms, it is synthesized in organs like kidneys, liver and pancreas. Its function is to store energy. After coming into being creatine is transported by blood to the brain and muscles where its concentration is the largest. That is where its name comes from- the Greek word *κρέας* [ˈkreas] which is translated as meat.

In muscles primary source of energy needed for the biochemical process is adenosine triphosphate (ATP). Unfortunately, it is an unstable molecule and cannot store energy. That function is performed by phosphocreatine. Phosphocreatine is created in a biochemical reaction where creatine receives one phosphoryl group from ATP (Creatine+ ATP→ phosphocreatine + ADP). In that form, energy is stored in muscles until is needed e.g. to conduct muscle contraction. In that situation reverse process is conducted: creatine and ATP are formed (phosphocreatine + ADP→ ATP + creatine). That process is catalyzed by creatine kinase (CK). Unexploited molecules of phosphocreatine fall apart and creatinine is formed which is eliminated with urine. Because of the way of excretion and their biochemical features creatinine in medicine is used as an index of renal function[1,2].

Exogenic creatine is delivered to the human body with food, especially meat where the concentration is the largest. Because of theoretical bases, it is common practice to intake creatine as a dietary supplement among professional and amateur sportsmen. Because of that, we decided to analyze recent scientific trials and try to answer the question if there are scientifically documented advantages of creatine supplementation. We decided to consider that problem on some levels. We divided our considerations depending on the target group (e.g. elderly population, sportsmen), and expected influence (e.g. body composition, cognitive functions). As medical professionals, we cannot omit the look of influence which creatine may have on the course of some diseases. We believe that our work summarizes scientific knowledge of the topic and brightens the true effects of creatine supplementation on human organisms.

Review method

We analyzed the newest research conducted from 2017 to 2024. The studies were searched in online databases like PubMed and Google Scholar. We focused on the impact of creatine supplementation on the elderly population, professional sportsmen, the course of some diseases, cognitive functions and body composition.

Use of creatine in professional sport

A 2017 article conducted a study on low-dose (0.03 g.kg.d^{-1}), short-term (14 days) oral supplementation of creatine monohydrate. For this, the researchers focused on a group of 19 elite youth soccer players aged around 17. They were members of the same team and had similar experience and seniority in training soccer. To date, they had never used additional supplementation or anabolic steroids. The study was conducted in the March-October period by dividing the players into two groups: one supplemented with creatine and the other got a placebo. The players were told to maintain their current dietary and training routines. Before the start of the study, the amount of body fat was measured, weighed and estimated based on skinfold thickness measurements in all subjects. The weakness of that study is that there was a difference between the studied groups. Players in the placebo group were significantly heavier than those in the creatine supplement group which creates complications in comparing the results of the two groups. In addition, the outcomes of the study are ambiguous. Peak power output (PPO) and mean power output (MPO) increased in players supplementing with creatine monohydrate but there were no significant differences in end-point data between the placebo and investigation groups. Natheless authors concluded that creatine has a positive effect on muscle outcomes. No side effects were noted[3].

Another publication investigated the effect of creatine on impact control in high-intensity interval training. High-intensity interval training is a specific workout that involves stressing the body with intense stimuli in different types of exercise. A group of eight elite soccer players aged about 16 years old was used to conduct the study. Their parameters were determined before the experiment began, and then they were divided into two groups: placebo supplementation and creatine supplementation. The experiment was conducted for 7 days during which the groups were supplemented with placebo and creatine. The results of the study show that physiological and biomechanical changes occurred in those supplementing creatine. Creatine can affect impact control during a single training session. Improvements in shock attenuation and impact control were also noted. In addition, the intensity of muscle activation during the pre-activation phase tended to decrease with creatine supplementation[4].

Another study examined the effects of creatine on the airways of youth elite athletes. Players from the Watford Football Club (FC) Academy were looked at for this purpose. Nineteen of them were under the age of 18 and nine under 21, all non-smokers. The subjects were randomly divided into two groups: creatine and placebo. Supplementation lasted for 8 weeks. The participants were examined before and after supplementation. Body weight and body composition (by measuring skin folds) were checked. Lung health tests such as spirometry, fractional exhaled nitric oxide (FENO) and the standard 6-min eucapnic voluntary hyperpnoea (EVH) test were also conducted. Participants were asked to make no changes in their daily routine and nutrition. Only 19 players completed the study: nine supplementing with creatine and 10 with placebo. One player reported gastrointestinal discomfort during the creatine supplementation period. There were no other side effects. After the experiment, there were no significant differences in body weight between the groups. However, there were significant changes in the body composition of the athletes. The thickness of skin folds decreased more in the creatine-supplemented group. There were no statistically significant differences in resting spirometry between the groups before or after supplementation. A statistical trend toward an unfavorable change after creatine supplementation was observed for FENO. The study did not show a significant effect of group or time on maximal FEV1 decline after EVH. The results suggest that creatine may affect the body composition of supplementers, but its possible negative effect on changes in FENO should be considered. Until further studies are conducted, creatine supplementation should be used with caution and respiratory status should be monitored[5].

Another study focused on testing the effects of creatine and β-hydroxy β-methylbutyrate (HMB) on athletes' performance. HMB is a metabolite of leucine, which is one of the three essential branched-chain amino acids. It can be used to increase muscle mass and skeletal muscle strength. In addition, it can also lower blood cortisol levels. Researchers hypothesized that the simultaneous use of creatine and HMB increases performance more than using these supplements separately. For the study, 28 elite male traditional rowers aged around 30 years old with similar physical conditions and similar physiques were gathered. They all performed the same training sessions for 6 days a week. Before starting the study, each participant was examined; none of them drank alcohol, smoked cigarettes, or took drugs or supplements other than those tested in the experiment. Participants were randomly divided into four groups: a placebo group, a creatine supplement group, an HMB supplement group, and a group supplementing both substances. Observations were carried out for 10 weeks. The results show that there were no significant differences in energy and micronutrient intake between the groups. In contrast, there was a significant decrease in muscle mass in the placebo group. The groups supplementing creatine, HMB and both experienced significant increases in absolute power output at the anaerobic threshold (WAT), with the largest increases occurring when creatine and HMB were supplemented simultaneously. The study leads us to believe that oral supplementation of creatine with HMB over 10 weeks of training shows a synergistic effect on aerobic power. Both supplements showed improvements in the incremental test, but simultaneous use produces even more favorable results[6].

Zając et al. focused on the effect of long-term creatine supplementation on sprinting ability in male soccer players. For this purpose, 20 elite soccer players were involved in the study, of which only 16 finished. The participants were divided into two groups: creatine supplementation and a placebo group. All were of similar age, with similar experiences. The ongoing study lasted 16 weeks. Analysis of variance (ANOVA) showed significant differences between baseline conditions and the four-time points in lactate concentration (LA) post-exercise. However, there were no statistically significant intra-group differences between the time points. The results of the study show that long-term supplementation with magnesium creatine chelate improved repeated sprint ability test (RAST) performance in elite soccer players. Compared to the placebo group, speed and power increased, as well as body mass and lean mass to a small extent. Importantly, the biggest difference was seen in the first four weeks of supplementation. After that time, creatine levels remained within reference values. It is worthwhile to continually study the effects of long-term supplementation because of possible new findings, as well as promising influence on performances of soccer players in modern sports which demands an increasing number of games being played in seasons[7].

The 2021 study focused on evaluating the effects of combined creatine and sodium bicarbonate supplementation on performance in elite soccer players. The study involved 20 players around the age of 20, who were divided into two groups: those supplementing creatine with sodium bicarbonate and a placebo group. All of them had not taken supplements in the past three months, had no injuries and were thoroughly examined. Performance tests consisting of 10m and 30m sprints, coordination tests and agility tests were conducted. In the 10m sprint tests, no differences were observed between the groups. Interestingly, in the case of the 30m sprints, the differences were already noticeable, with significantly faster times achieved by the group supplementing with creatine and sodium bicarbonate. The agility test also went favorably for those taking the supplements. The agility time decreased after 7 days of supplementation, while it did not change in the placebo group. It can therefore be concluded that creatine and sodium bicarbonate supplementation improves sprinting and agility in elite soccer players.

However, it is not possible to say conclusively which supplement this is due to, or whether simultaneous use induces synergy. This opens the door to further research in the future[8].

Another study examined whether the supplement intake in different parts of the day influences outcomes. For this purpose, a study was conducted on 14 female handball players between the ages of 18 and 35. They were randomly divided into two groups, both of which took creatine at the same dose but half of the participants in the morning and the other half in the evening. The entire study lasted 12 weeks. All female athletes were examined during the first and last week. There were no significant differences in body composition or any study variable between the two groups at the beginning of the study. After 12 weeks, a reduction in the percentage of body fat was observed only in the morning group. Improvements in strength were observed in both groups. The results suggest that creatine has a positive effect on improving athletic performance in elite female handball players. Morning creatine intake may affect fat reduction. However, no differences in performance were observed between morning and evening creatine intake[9].

Effects of creatine supplementation on an ageing population

Candow et al.[10] investigated the effect of pre-exercise and post-exercise creatine supplementation on bone mineral content and density in healthy ageing adults. Thirty-nine participants (over 50 years old) were divided into three groups: creatine before resistance training, creatine after resistance training, and placebo group. Whole-body resistance training was performed 3 days a week for 8 months. Before and following the experiment, bone mineral content and density of the whole body, limbs, femoral neck, lumbar spine, and total hip were determined by dual-energy X-ray absorptiometry. The authors concluded that creatine supplementation did not affect ageing bone mineral content or density, neither before training nor after. Although the above, this study had some limitations: the incorporation of ageing males and females probably influenced the results, dual-energy X-ray absorptiometry measured only areal changes in bone minerals, the dietary calcium or vitamin D intake was not assessed, and bone turnover or the mechanistic actions of creatine on bone were not measured.

Similar conclusions were formulated by Sales et al.[11] in their experiment. During a 2-year randomized, placebo-controlled trial, 200 postmenopausal women (>70 years old) with osteopenia supplemented 3 g/day of creatine. Areal bone mineral density, lean and fat mass, volumetric bone mineral density (BMD) and bone microarchitecture parameters, biochemical bone markers, physical function and strength were assessed at baseline and after 12 and 24 months. In comparison to the control group with placebo, there was no improvement in bone health or muscle function. This study also had some limitations: the results were associated with elderly women with osteopenia and should not be generalized to other conditions. Moreover, none of the participants was regularly engaged in resistance training.

In another experiment, the effects of different creatine supplementation dosages on ageing muscle performance and functionality were compared. Thirty-three participants (58,5 +/- 4,7 years old) were randomized to one of three groups: creatine-high (0,3 g/kg/day of creatine + 0,1 g/kg/day of maltodextrin), creatine moderate (0,1 g/kg/day of creatine + 0,3 g/kg/day of maltodextrin) or placebo (0,4 g/kg/day of maltodextrin) for 10 consecutive days. Muscle strength, muscle endurance, and physical performance (dynamic balance) were measured at baseline and after supplementation. In that experiment, Chami et al.[12] proved that creatine supplementation, independent of dosage and resistance training, did not affect ageing muscle performance. There were several limitations to this study: small number of participants, no measure of habitual dietary intake, or inability to assess responders and non-responders to creatine supplementation because muscle biopsies were not performed.

In another study, Candow et al.[13] investigated the long-term effects of creatine supplementation and resistance training on bone mineral density and bone geometric properties in older males (≥49 years of age). The first group of 18 participants was supplemented with 0,1 g/kg/day of creatine, and the second group of 20 participants took placebo. As a result, after 12 months authors concluded that both groups experienced similar changes in bone mineral density and geometry, bone speed of sound, lean tissue and fat mass, muscle thickness, and muscle strength. Creatine supplementation and supervised, whole-body resistance training had no greater effect on measures of bone, muscle, or strength in older males compared with placebo. Although the above, this study presented some limitations: important variables, like initial intramuscular creatine levels or habitual dietary, which may have included the results, were not assessed.

On the other hand, another study showed different results. Bernat et al.[14] investigated the effects of high-velocity resistance training and creatine supplementation in untrained healthy aging males (≥50 years old). The participants were randomized to supplement with creatine (0,1 g/kg/day of creatine + 0,1 g/kg/day of maltodextrin) and placebo (0,2 g/kg/day of maltodextrin) for 8 weeks. Before and following the training, muscle strength, muscle thickness, peak torque and physical performance were assessed. The authors proved that not only high-volume resistance training increases muscle strength, muscle thickness, and some measures of peak torque and physical performance in untrained healthy ageing males, but also the addition of creatine supplementation leads to gains in leg press and total lower-body strength. Despite several limitations in this study like initial intramuscular creatine concentrations were not assessed, the dietary was not controlled, and the consumption of creatine was not supervised on non-training days, the outcomes are promising.

During the 2-year randomized controlled trial, Chilibeck et al.[15] proved that creatine supplementation and resistance training/walking program in a group of 237 postmenopausal women (approximately 59 years old) did not affect bone mineral density, but it improved bone geometric properties at the proximal femur (increased cortical thickness and section modulus). The participants were divided into two groups: in the first one, women received 0,14 g/kg/day of creatine and in the second one they received a placebo. The results in the experimental group presented no significant differences in comparison to the placebo group, except for some bone geometric properties at the proximal femur in the creatine group. These results suggest that these bone changes may be protective against hip fracture, although more research should be performed.

A similar experiment was conducted by Amiri et al.[16]. The authors evaluated the effect of resistance training and creatine supplementation on oxidative stress, antioxidant defense, muscle strength, and quality of life in older adults (mean 68,1 years old). The participants were divided into three groups: resistance training with creatine supplementation (0,1 g/kg/day), resistance training with placebo (starch) and control group. After 10 weeks of the trial, the authors concluded that regular resistance training may improve the antioxidant body system, muscle strength and quality of life. Creatine in addition to exercises might double the amount of strength gained from resistance training but probably has no role in the antioxidant system and quality of life.

Seper et al.[17] checked the impact of 8-week guanidinoacetate-creatine (GAA-creatine) supplementation versus placebo on skeletal muscle and brain creatine levels, cognitive function, functional outcomes, and safety biomarkers like clinical enzymes, total protein, blood area nitrogen, creatinine and C-reactive protein in men and women aged ≥65 years. Participants were divided into two groups: the first one was supplemented with 2 g/day of GAA and 2 g/day of creatine, in the second one was supplemented with inulin. In this trial, co-administration of GAA and creatine significantly improved concentrations of the brain and muscle creatine, and functional mobility outcomes compared with a placebo intervention, which suggests that the older population can benefit from creatine supplementation but further studies need to be conducted.

Oliveira et al.[18] investigated the additional effect of creatine supplementation on inflammation and insulin resistance in a group of 32 healthy, non-athletic older adults aged 60-80 years. The participants were assigned to two different groups: one with creatine supplementation (5 g/day) combined with resistant training, and the second with placebo (5g /day of maltodextrin) combined with resistant training. After 12 weeks, blood samples were collected for glucose, insulin, adiponectin, leptin, interleukin 6, interleukin 10, monocyte chemo-attractant protein-1 and C-reactive protein analysis and were compared to blood test performed in baseline. There were no differences between groups in any of the variables analyzed. Only monocyte chemoattractant protein 1 was reduced in both groups, regardless of creatine supplementation. The limitations of this experiment include a small group of inflammatory markers that were assessed. More biomarkers of muscle biochemistry and muscle damage should be analyzed.

All of the experiments were conducted on ageing adults, although different aspects were investigated. The impact of creatine supplementation on muscle and skeletal system, the levels of glucose, cognitive function or inflammation is still controversial. Because of study limitations, the necessity of more research should be highlighted.

Influence of creatine on selected diseases

J. Slankamenac and co-authors conducted an eight-week randomized trial on creatine and glucose supplementation during long COVID-19. The study included 15 adult patients suffering from long COVID-19 with moderate fatigue and at least one additional symptom. Patients were divided into 3 experimental groups. Group 1 received 8g of creatine monohydrate daily, group 2 received a mixture of 8g of creatine monohydrate and 3g of glucose daily, and group 3 received 3g of glucose daily. Total creatine concentrations were assessed using magnetic resonance spectroscopy in the medial vastus muscle and thalamus, frontal, precentral, medial, and parietal white and gray matter of the brain. Fatigue was also assessed using the Multidimensional Fatigue Inventory (MFI-20) and the severity of long COVID symptoms using a visual analog scale (VAS). No adverse events or side effects were observed during the study. There were no significant changes in creatine levels in the control group. During the eight-week study, it was found that taking creatine with or without glucose was well tolerated, resulting in increased tissue creatine levels compared to the control sample. Finally, there was a significant improvement and reduction in symptoms of the disease. Long COVID is characterized by a reduced amount of creatine in the tissues, so supplementation with exogenous creatine may be recommended as an effective method of correcting deficiencies and thus reducing symptoms of the disease[19].

Another randomized study investigated the effect of 7-day short-term creatine supplementation and its impact on muscle performance in breast cancer (BC) survivors. A double-blind study of 19 women was conducted. 9 of the women were assigned to the creatine treatment group, while the other 10 were assigned to the dextrose placebo group. Many tests were assessed during the study, including the strength of standing up from a seated position, balance, standing on a chair, walking speed, standing up and walking for a time, and 10 repetitions of the maximum (10RM) for chest press and leg extensions. Potential differences in responses of participants to creatine loading, the chosen set of tests, and/or the time needed to recover during or between tests were noted, which contributed to the conclusion that short-term keratin supplementation did not show ergogenic effects on neuromuscular performance in subjects treated for breast cancer. A potential explanation for the lack of differences during the study may be the variability in response to creatine supplementation (intramuscular creatine stores were not measured in the above study so it is not determined). Another potential reason for the lack of variation in the study may be the phenotype of "accelerated ageing" in breast cancer patients and those receiving chemotherapy, in addition, such patients have a blunted response to physical training. The population of study subjects 79% had previously received chemotherapy which may be the reason for the lack of significant results during the study[20].

The influence of creatine supplementation on renal function in patients with peripheral artery disease was studied. During the eight-week study, creatine supplementation was given to 14 of the twenty-nine contestants. The remaining 15 received a placebo. Creatine was administered in a regimen: loading phase: 1 week of 20g/day followed by maintenance phase: 7 weeks at a daily dose of 5g. Markers of renal function, serum creatinine concentration, creatinine excretion rate and creatinine clearance were analyzed before and after the supplementation period. When the results were analyzed, there were no significant differences between the groups, which indicates that creatine supplementation is safe and does not adversely affect renal function in patients diagnosed with peripheral artery disease[21].

While conducting another randomized trial, the effect of creatine supplementation on functional capacity (walking ability) and calf muscle oxygen saturation in patients with symptomatic peripheral artery disease was verified. The study was completed by 29 patients of both sexes divided in a double-blind fashion into two groups (one receiving a placebo and the other creatine monohydrate). The study was divided into a loading phase (20g/day for 1 week) and a maintenance phase (5g/day for 7 weeks), in addition, patients were advised to increase their physical activity levels in accordance with vascular disease guidelines. During the study, a 6-minute walk test was assessed as the primary outcome; the secondary outcome was calf muscle oxygen saturation. The results of the study show that patients taking creatine had higher plasma levels of creatine than in the placebo group, but creatine content in muscle was not measured so the effect of supplementation on muscle concentration was not determined. The results show that creatine does not increase functional capacity or calf muscle oxygen saturation in patients with symptomatic peripheral artery disease. Although the above study shows safety creatin in peripheral artery disease it seems that there are no positive effects on symptoms [22].

S. Dover et al. in their study described the effect of creatine supplementation on muscle function in juvenile dermatomyositis. The study also aimed to determine the effect of creatine on muscle function and metabolism, aerobic capacity, fatigue, physical activity and quality of life. The study was conducted for 6 months in a randomized, double-blinded fashion in patients aged 7-18 years. Muscle function, aerobic capacity and muscle strength were assessed using standardized exercise tests. Muscle metabolism was assessed by 31-phosphate magnetic resonance spectroscopy. Questionnaires were used to assess fatigue, physical activity and quality of life. The study showed no therapeutically significant effects when analyzing physical function, aerobic capacity, disease activity, fatigue, physical activity or quality of life. Better muscle metabolism results were obtained, which were confirmed by the exercise test. Analyzing the results, it can be concluded that creatine supplementation in children with dermatomyositis is safe and well tolerated as well as can lead to improvement of muscle metabolism[23].

Another study of creatine and ribose supplementation along with an exercise program was designed to determine whether they would improve total exercise capacity in a population of patients diagnosed with ischemic heart disease. Fifty-three patients underwent a double-blind, randomized study lasting six months. Patients were divided into groups that received either a placebo or a nutraceutical composition containing creatinine, D-ribose, vitamin B1 and B6. During the study, the maximum load tolerated during an exercise test on a bicycle ergometer, body composition in % FM (fat mass), free fat mass, % water, blood analysis with lipid profile, blood glucose and creatinine were analyzed. It was noted that after 6 months of the study, double peak cardiac product, double delta product and chronotropic index were higher in the active treatment group than in the placebo group. Based on the study, it can be concluded that supplementation with creatine, D-ribose, vitamin B1 and B6 has positive effects on exercise tolerance in people diagnosed with ischemic heart disease[24].

Influence of creatine on cognitive functions

A study conducted by Mabrey et al.[25] is a double-blind, randomized, crossover trial that examines the effect of creatine nitrate and caffeine individually and combined on cognitive and physical functions. The performance of twelve resistance-trained male athletes was assessed before and after seven days of creatine nitrate(5g/day), caffeine(400mg/day) and a combination of creatine nitrate and caffeine supplementation. Next, they performed standardized resistance exercises- leg and bench press at 70% one repetition maximum, Wingate anaerobic power test, cognitive-Stroop Word-Color Test and cardiovascular responses (45min after supplementation). It was shown that creatine nitrate and caffeine co-ingested significantly improved cognitive function and this combination was more effective than caffeine alone in enhancing cognitive performance. No significant improvements in exercise performance were observed. It seems that seven days of simultaneous creatine nitrate and caffeine intake improves cognition functions without noticing any side effects.

Van Cutsem et al.[26] also used the Stroop task in the evaluation of creatine abilities to alter cognitive state. Fourteen healthy participants performed (90 minutes) a mentally fatiguing task after seven days of creatine supplementation (20g/d), and after seven days of placebo supplementation- in between there was five weeks long washout period. In both conditions, a 7-minute sport-specific visuomotor task, a 3-minute Flanker task and a dynamic handgrip strength endurance task were performed before and after the mentally fatiguing task. The results show that accuracy on the Stroop task and handgrip strength endurance was higher on creatine compared to placebo. In other parameters, there was no significant improvement.

Another study by Samadi et al.[27] compared the effects of seven days of creatine addition at the end of four weeks of beta-alanine (BA) supplementation compared to BA alone. Twenty male military personnel were randomized into two groups: BA + creatine or BA + placebo. Both groups were supplemented with 6.4g/day BA for 28 days. After 3 weeks in BA + creatine group supplementation with creatine (0.3g/kg/day) was added and the BA + placebo took an isocaloric placebo for a week. Before and after supplementation each contestant performed a series of physical and cognitive tests and also provided a venous blood sample. In the BA + creatine group, there was a significant improvement in physical performance and mathematical processing over time, while there was no change in the BA + placebo group. Vertical jump and testosterone levels were significantly higher in BA + creatine compared to BA + placebo. It appears that creatine addition during the final week of 4 weeks of BA supplementation improves muscular and cognitive performance and shows better results than BA alone.

Sandkühler et al.[28] conducted big preregistered, cross-over, double-blind, placebo-controlled and randomized study with creatine (5g/day) supplementation for 6 weeks on 123 adult participants. Half of them were vegetarian and half were omnivores. Participants were tested on Backward Digit Span (BDS) and Raven's Advanced Progressive Matrices (RAPM) as well as eight exploratory cognitive tests. The results of the creatine group bordered significance for BDS but in RAMP there were no significant changes. There was no noticeable improvement in exploratory cognitive tasks. Vegetarians did not benefit more from creatine than omnivores. Side effects were significantly more often reported for creatine than placebo.

Creatine supplementation effects on body composition

A study that measured body composition after creatine supplementation was conducted on 27 healthy young adults [29]. 14 women and 13 males completed one week of creatine monohydrate (0.3g/kg/d) or maltodextrin loading protocol. Participants had their body composition analyzed before and after supplementation using dual-energy X-ray absorptiometry (DEXA), single-frequency bioelectrical impedance (SF-BIA), and multi-frequency bioelectrical impedance (MF BIA) to measure body fat percentage (BF%), fat free mass (FFM), and fat mass (FM). Furthermore, intracellular water (ICW), extracellular water (ECW) and total body water (TBW) were estimated by MF-BIA. FFM significantly increased more in the creatine group than in the control group measured by all three devices. The group with creatine supplementation noticed a significant increase in TBW measured by MF-BIA. MF-BIA, SF-BIA and DEXA noticed changes in TBW following one week of creatine supplementation due to an increase in FFM.

Another trial examined changes in fluid distribution across menstrual phases with creatine supplementation[30]. 30 moderately active females, menstruating naturally or using hormonal contraceptives were picked randomly to the creatine group taking 5g of creatine monohydrate four times a day or a placebo group. Body mass (BM), TBW, ICW, and ECW were measured before and after supplementation. There was no significant difference in BM changes between the intervention and placebo groups regardless of menstrual cycle phases. There were no significant differences between naturally menstruating and women using birth control. A significant increase was observed in TBW, ICW and ECW following luteal phase supplementation.

A similar study by Brooks et al.[31] also demonstrated a significant increase in TBW and lean mass in the creatine group (0.1g/kg/day + 0.1/kg/day maltodextrin) in contrast to the placebo group (0.2g/kg/day maltodextrin) after 42 days of supplementation in female collegiate dancers.

Marini et al.[32] compared effects of creatine supplementation on body composition and Malnutrition-Inflammation Score (MIS) in patients with chronic kidney disease (CKD) undergoing hemodialysis. This study consisted of 40 patients divided into two groups: creatine group (received 5g of creatine monohydrate and 5g of maltodextrin/day)- 21 patients or placebo group (received 10g of maltodextrin/ day)- 19 patients. MIS and body composition were analyzed three times: before, after 6 months and after 12 months of creatine and placebo intake. In the creatine group, there was a significant increase in BM, FFM, skeletal muscle mass index (SMMI), TBW and ICW. Changes in FFM and SMMI may be connected by elevating ICW. Long-term creatine supplementation in dialysis patients did not change MIS.

Discussion

The studies, which we have taken cognizance of, show that creatine supplementation is beneficial in professional sports, can improve the course of some diseases and improve muscle strength in the aging population. It can also enhance cognitive functions as well as lead to changes in body composition. Some effects of creatine supplementation are still controversial and further investigation is needed to determine its usefulness. Although creatine seems to be a safe and usually well-tolerated substance even in high doses in healthy populations, its safety in renal diseases is controversial[33,34].

Sport professionals can improve their power output by creatine supplementation[3,6,7]. It seems that oral intake of creatine leads to some beneficial biomechanical changes during high-intensity interval training, that can make it safer to perform[4]. Kim et al. concluded that creatine and sodium bicarbonate supplementation improves sprinting and agility in elite soccer players[8].

The authors of another study suggested that creatine has a positive effect on improving athletic performance in elite female handball players, regardless of the time of day of creatine consumption. What is more fat reduction is more noticeable by morning intake[9]. Despite the general safety of creatine, Simpson et al. pointed out some controversies when it comes to the impact of creatine on lung conditions measured by fractional exhaled nitric oxide[5]. Cited papers regarding professional sports have some weak points such as small groups of contestants who often were from similar environments e.g. the same sports club, and were similar in age. We hope that bigger trials on a wider population will be performed to examine the impact of creatine supplementation on sports professionals.

Some authors concluded that creatine does not have an impact on bone density in the ageing population[10,11,13,15], so hopes to have another agent to fight osteopenia were dashed. Creatine short-term supplementation in addition to resistance training is potentially beneficial in improving muscle function[14,16] but in the long term it does not seem to be playing an important role[13]. Chami et al.[12], Sales et al.[11] proved that creatine supplementation without resistance training, did not affect aging muscle performance. These publications point out that physical training is crucial to improving muscle function and cannot be replaced by creatine usage. All the same, creatine can boost its effect. Some results suggest that bone geometry changes due to a combination of training and creatine supplementation may be protective against hip fracture, although more research should be performed[15]. Seper et al.[17] pointed out that creatine can significantly improve mobility outcomes compared with a placebo intervention. Oliveira et al.[18] concluded that creatine supplementation does not affect insulin resistance and inflammation as an addition to resistance training. All of the experiments were conducted on ageing adults, although different aspects were investigated. The impact of creatine supplementation on muscle and skeletal system, the levels of glucose, cognitive function or inflammation is still controversial. Because of study limitations, the necessity of more research should be highlighted.

J. Slankamenac noticed a significant improvement and reduction in symptoms occurring in the long COVID[19]. Long COVID is characterized by a reduced amount of creatine in the tissues, so supplementation with exogenous creatine may be recommended as an effective method of correcting deficiencies and thus reducing symptoms of the disease. Short-term creatine supplementation without monitored training did not show ergogenic effects on neuromuscular performance in subjects treated for breast cancer[20]. We hope that another trial will combine creatine supplementation with an exercise program to check if creatine could potentially help during the rehabilitation of breast cancer survivors. The results of another study show that creatine does not increase functional capacity or calf muscle oxygen saturation in patients with symptomatic peripheral artery disease as well as does not adversely affect renal function in this population[21,22] Analyzing the results of the trial performed by Dover et al., it can be concluded that creatine supplementation in children with dermatomyositis is safe and well tolerated as well as can lead to improvement of muscle metabolism[23]. Derosa et al. concluded that supplementation with creatine, D-ribose, vitamin B1 and B6 has positive effects on exercise tolerance in people diagnosed with ischemic heart disease[24]. These results are promising because enhancing exercise tolerance can make rehabilitation easier and more comfortable for patients with ischemic heart disease.

Mabrey et al. concluded that creatine nitrate and caffeine co-ingested significantly improved cognitive function and this combination was more effective than caffeine alone in enhancing cognitive performance[25]. Another trial showed that short-term creatine supplementation improved visuomotor skills investigated by the Stroop test[26]. It appears that creatine addition during the final week of 4 weeks of beta-alanine supplementation improves muscular and cognitive performance and shows better results than beta-alanine alone[27]. Sandkühler et al. performed a study where creatine only improved results on Backward Digit Span on the verge of statistical significance, while there were no significant differences in other cognitive tests so the role of creatine in enhancing cognitive functions is controversial[28]. As we can see, the results of cited trials are not consistent when it comes to the effects of creatine on cognitive functions and further studies need to be performed.

Authors made consistent conclusions regarding the impact of creatine supplementation on increasing total body water[29–32]. Creatine also led to the growth of fat-free mass[29,32]. Long-term creatine supplementation in hemodialysis patients elevated fat-free mass and skeletal muscle mass index, which was probably due to an increase in intracellular water[32].

Conclusions

Creatine supplementation is beneficial in professional sports, can improve the course of some diseases and improve muscle strength in the ageing population. It can also enhance cognitive functions as well as lead to changes in body composition. Some effects of creatine supplementation are still controversial and further investigation is needed to determine its usefulness.

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Conflicts of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

1. Bańkowski E et al., Biochemistry. Chapters: 6.1.3; 19.5.11;21.2; 37.2.4, 4th ed. Edra Urban & Partner, Wrocław 2020.
2. Stolnica B et al., Laboratory diagnostics with clinical biochemistry. Chapter: Laboratory diagnostics of kidneys, 5th ed. Edra Urban & Partner, Wrocław 2022.

3. Yáñez-Silva A, Buzzachera CF, Piçarro IDC, Januario RSB, Ferreira LHB, McAnulty SR, Utter AC, Souza-Junior TP. Effect of low dose, short-term creatine supplementation on muscle power output in elite youth soccer players. J Int Soc Sports Nutr. 2017;14:5. https://doi.org/10.1186/s12970-017-0162-2
4. da Silva Azevedo AP, Michelone Acquesta F, Lancha AH Jr, Bertuzzi R, Poortmans JR, Amadio AC, Cerca Serrão J. Creatine supplementation can improve impact control in high-intensity interval training. Nutrition. 2019;61:99-104. https://doi.org/10.1016/j.nut.2018.09.020
5. Simpson AJ, Horne S, Sharp P, Sharps R, Kippelen P. Effect of Creatine Supplementation on the Airways of Youth Elite Soccer Players. Med Sci Sports Exerc. 2019;51:1582–1590. https://doi.org/10.1249/mss.0000000000001979
6. Fernández-Landa J, Fernández-Lázaro D, Calleja-González J, Caballero-García A, Córdova Martínez A, León-Guereño P, Mielgo-Ayuso J. Effect of Ten Weeks of Creatine Monohydrate Plus HMB Supplementation on Athletic Performance Tests in Elite Male Endurance Athletes. Nutrients. 2020;12(1):193. https://doi.org/10.3390/nu12010193
7. Zajac A, Golas A, Chycki J, Halz M, Michalczyk MM. The Effects of Long-Term Magnesium Creatine Chelate Supplementation on Repeated Sprint Ability (RAST) in Elite Soccer Players. Nutrients. 2020;12(10):2961. https://doi.org/10.3390/nu12102961
8. Kim J. Effects of Combined Creatine and Sodium Bicarbonate Supplementation on Soccer-Specific Performance in Elite Soccer Players: A Randomized Controlled Trial. Int J Environ Res Public Health. 2021;18(13):6919. https://doi.org/10.3390/ijerph18136919
9. Jurado-Castro JM, Campos-Pérez J, Vilches-Redondo MÁ, Mata F, Navarrete-Pérez A, Ranchal-Sanchez A. Morning versus Evening Intake of Creatine in Elite Female Handball Players. Int J Environ Res Public Health. 2021;19(1):393. https://doi.org/10.3390/ijerph19010393
10. Candow DG, Forbes SC, Vogt E. Effect of pre-exercise and post-exercise creatine supplementation on bone mineral content and density in healthy aging adults. Exp Gerontol. 2019;119:89-92. https://doi.org/10.1016/j.exger.2019.01.025
11. Sales LP, Pinto AJ, Rodrigues SF, Alvarenga JC, Gonçalves N, Sampaio-Barros MM, Benatti FB, Gualano B, Rodrigues Pereira RM. Creatine Supplementation (3 g/d) and Bone Health in Older Women: A 2-Year, Randomized, Placebo-Controlled Trial. J

Gerontol A Biol Sci Med Sci. 2020;75(5):931-938. https://doi.org/10.1093/gerona/glz162

12. Chami J, Candow DG. Effect of Creatine Supplementation Dosing Strategies on Aging Muscle Performance. J Nutr Health Aging. 2019;23(3):281-285. https://doi.org/10.1007/s12603-018-1148-8
13. Candow DG, Chilibeck PD, Gordon J, Vogt E, Landeryou T, Kaviani M, Paus-Jensen L. Effect of 12 months of creatine supplementation and whole-body resistance training on measures of bone, muscle and strength in older males. Nutr Health. 2021;27(2):151-159. https://doi.org/10.1177/0260106020975247
14. Bernat P, Candow DG, Gryzb K, Butchart S, Schoenfeld BJ, Bruno P. Effects of high-velocity resistance training and creatine supplementation in untrained healthy aging males. Appl Physiol Nutr Metab. 2019;44(11):1246-1253. https://doi.org/10.1139/apnm-2019-0066
15. Chilibeck PD, Candow DG, Gordon JJ, Duff WRD, Mason R, Shaw K, Taylor-Gjevre R, Nair B, Zello GA. A 2-yr Randomized Controlled Trial on Creatine Supplementation during Exercise for Postmenopausal Bone Health. Med Sci Sports Exerc. 2023;55(10):1750-1760. https://doi.org/10.1249%2FMSS.0000000000003202
16. Amiri E, Sheikholeslami-Vatani D. The role of resistance training and creatine supplementation on oxidative stress, antioxidant defense, muscle strength, and quality of life in older adults. Front Public Health. 2023;11:1062832. https://doi.org/10.3389/fpubh.2023.1062832
17. Seper V, Korovljev D, Todorovic N, Stajer V, Ostojic J, Nesic N, Ostojic SM. Guanidinoacetate-Creatine Supplementation Improves Functional Performance and Muscle and Brain Bioenergetics in the Elderly: A Pilot Study. Ann Nutr Metab. 2021;77(4):244-247. https://doi.org/10.1159/000518499
18. Oliveira CLP, Antunes BMM, Gomes AC, Lira FS, Pimentel GD, Boulé NG, Mota JF. Creatine supplementation does not promote additional effects on inflammation and insulin resistance in older adults: A pilot randomized, double-blind, placebo-controlled trial. Clin Nutr ESPEN. 2020;38:94-98. https://doi.org/10.1016/j.clnesp.2020.05.024
19. Slankamenac J, Ranisavljev M, Todorovic N, Ostojic J, Stajer V, Candow DG, Ratgeber L, Betlehem J, Acs P, Ostojic SM. Eight-Week Creatine-Glucose Supplementation Alleviates Clinical Features of Long COVID. J Nutr Sci Vitaminol (Tokyo). 2024;70(2):174-178. https://doi.org/10.3177/jnsv.70.174

20. Parsowith EJ, Stock MS, Kocuba O, Schumpp A, Jackson K, Brooks AM, Larson A, Dixon M, Fairman CM. Impact of Short-Term Creatine Supplementation on Muscular Performance among Breast Cancer Survivors. Nutrients. 2024;16(7):979. https://doi.org/10.3390/nu16070979
21. Domingues WJR, Ritti-Dias RM, Cucato GG, Wolosker N, Zerati AE, Puech-Leão P, Nunhes PM, Moliterno AA, Avelar A. Does Creatine Supplementation Affect Renal Function in Patients with Peripheral Artery Disease? A Randomized, Double Blind, Placebo-controlled, Clinical Trial. Ann Vasc Surg. 2020;63:45-52. https://doi.org/10.1016/j.avsg.2019.07.008
22. Domingues WJR, Ritti-Dias RM, Cucato GG, Wolosker N, Zerati AE, Puech-Leão P, Coelho DB, Nunhes PM, Moliterno AA, Avelar A. Effect of Creatine Supplementation on Functional Capacity and Muscle Oxygen Saturation in Patients with Symptomatic Peripheral Arterial Disease: A Pilot Study of a Randomized, Double-Blind Placebo-Controlled Clinical Trial. Nutrients. 2021;13(1):149. https://doi.org/10.3390/nu13010149
23. Dover S, Stephens S, Schneiderman JE, Pullenayegum E, Wells GD, Levy DM, Marcuz JA, Whitney K, Schulze A, Tein I, Feldman BM. The Effect of Creatine Supplementation on Muscle Function in Childhood Myositis: A Randomized, Double-blind, Placebo-controlled Feasibility Study. J Rheumatol. 2021;48(3):434-441. https://doi.org/10.3899/jrheum.191375
24. Derosa G, Pasqualotto S, Catena G, D'Angelo A, Maggi A, Maffioli P. A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Effectiveness of a Food Supplement Containing Creatine and D-Ribose Combined with a Physical Exercise Program in Increasing Stress Tolerance in Patients with Ischemic Heart Disease. Nutrients. 2019;11(12):3075. https://doi.org/10.3390/nu11123075
25. Mabrey G, Koozehchian MS, Newton AT, Naderi A, Forbes SC, Haddad M. The Effect of Creatine Nitrate and Caffeine Individually or Combined on Exercise Performance and Cognitive Function: A Randomized, Crossover, Double-Blind, Placebo-Controlled Trial. Nutrients. 2024;16(6):766. https://doi.org/10.3390/nu16060766
26. VAN Cutsem J, Roelands B, Pluym B, Tassignon B, Verschueren JO, DE Pauw K, Meeusen R. Can Creatine Combat the Mental Fatigue-associated Decrease in Visuomotor Skills? Med Sci Sports Exerc. 2020;52(1):120-130. https://doi.org/10.1249/mss.0000000000002122

27. Samadi M, Askarian A, Shirvani H, Shamsoddini A, Shakibaee A, Forbes SC, Kaviani M. Effects of Four Weeks of Beta-Alanine Supplementation Combined with One Week of Creatine Loading on Physical and Cognitive Performance in Military Personnel. Int J Environ Res Public Health. 2022;19(13):7992. https://doi.org/10.3390/ijerph19137992
28. Sandkühler JF, Kersting X, Faust A, Königs EK, Altman G, Ettinger U, Lux S, Philipsen A, Müller H, Brauner J. The effects of creatine supplementation on cognitive performance-a randomised controlled study. BMC Med. 2023;21(1):440. https://doi.org/10.1186/s12916-023-03146-5
29. Buck EA, Saunders MJ, Edwards ES, Womack CJ. Body composition measured by multi-frequency bioelectrical impedance following creatine supplementation. J Sports Med Phys Fitness. 2023;63(11):1188-1193. https://doi.org/10.23736/s0022-4707.23.15058-4
30. Moore SR, Gordon AN, Cabre HE, Hackney AC, Smith-Ryan AE. A Randomized Controlled Trial of Changes in Fluid Distribution across Menstrual Phases with Creatine Supplementation. Nutrients. 2023;15(2):429. https://doi.org/10.3390/nu15020429
31. Brooks SJ, Candow DG, Roe AJ, Fehrenkamp BD, Wilk VC, Bailey JP, Krumpl L, Brown AF. Creatine monohydrate supplementation changes total body water and DXA lean mass estimates in female collegiate dancers. J Int Soc Sports Nutr. 2023;20(1):2193556. https://doi.org/10.1080/15502783.2023.2193556
32. Marini ACB, Schincaglia RM, Candow DG, Pimentel GD. Effect of Creatine Supplementation on Body Composition and Malnutrition-Inflammation Score in Hemodialysis Patients: An Exploratory 1-Year, Balanced, Double-Blind Design. *Nutrients*. 2024; 16(5):615. https://doi.org/10.3390/nu16050615
33. Kim HJ, Kim CK, Carpentier A, Poortmans JR. Studies on the safety of creatine supplementation. Amino Acids. 2011;40(5):1409-1418. https://doi.org/10.1007/s00726-011-0878-2
34. Bender A, Klopstock T. Creatine for neuroprotection in neurodegenerative disease: end of story?. Amino Acids. 2016;48(8):1929-1940. https://doi.org/10.1007/s00726-015-2165-0