MĄDRY, Wojciech, MAZURKIEWICZ, Aleksandra, MARCICKA, Justyna, KOŁODZIEJ, Magdalena, MĘCZYŃSKA, Joanna, SAIUK, Nazarii, KOZICZ, Michał Andrzej, SEREDYŃSKI, Tomasz, WOJCIECHOWSKA, Adriana and SALASA, Weronika. Creatine - new hope in cancer treatment. Journal of Education, Health and Sport. 2024;66:50077. eISSN 2391-8306.
https://dx.doi.org/10.12775/JEHS.2024.66.005
https://apcz.umk.pl/JEHS/article/view/50077
https://zenodo.org/records/10996690

**The journal has had 40 points in Minister of Science and Higher Education of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).
Punkty Ministerialne 40 punktów. Załącznik do komunikatu Ministra Nauki i Szkolnictwa Wyższego z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).
The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 28.03.2024. Revised: 10.04.2024. Accepted: 15.04.2024. Published: 19.04.2024.

Creatine - new hope in cancer treatment

1. Wojciech Mądry [WM]
   Ludwik Rydygier Specialist Hospital in Kraków, Złotej Jesieni 1 Estate, 31-826 Kraków
   https://orcid.org/0009-0003-9434-0478
   madry.mw@gmail.com
2. Aleksandra Mazurkiewicz [AM]
   Ludwik Rydygier Specialist Hospital in Kraków, Złotej Jesieni 1 Estate, 31-826 Kraków
   https://orcid.org/0009-0008-9427-9378
   aleksamazurkiewicz@gmail.com
3. Justyna Marcicka [JM]
   Ludwik Rydygier Specialist Hospital in Kraków, Złotej Jesieni 1 Estate, 31-826 Kraków
   https://orcid.org/0009-0003-1766-7397
   justyna.marcicka@gmail.com
4. Magdalena Kołodziej [MK]
   Brothers Hospitallers Hospital in Kraków, Trynitarska 11, 31-061 Kraków
   https://orcid.org/0000-0002-6597-1559
   magdalenakolodziej502@gmail.com

5. Joanna Męczyńska [JM]
   St. John Paul II Mazovian Provincial Hospital in Siedlce, Poland, Księcia Józefa Poniatowskiego 26, 08-110 Siedlce
   https://orcid.org/0009-0002-0292-8032
   joanna.meczynska@gmail.com
6. Nazarii Saiuk [NS]
   Ludwik Rydygier Specialist Hospital in Kraków, Złotej Jesieni 1 Estate, 31-826 Kraków
   https://orcid.org/0000-0001-6722-0751
   nazarii.saiuk@gmail.com
7. Michał Andrzej Kozicz [MAK]
   Brothers Hospitallers Hospital in Kraków, Trynitarska 11, 31-061 Kraków
   https://orcid.org/0009-0001-4254-4087
   kozicz.michal@gmail.com
8. Tomasz Seredyński [TS]
   St. Lucas Provincial Hospital Tarnów, Lwowska 178A, 33-100 Tarnów
   https://orcid.org/0009-0000-7806-0220
   tomasz.seredynski98@gmail.com
9. Adriana Wojciechowska [AW]
   The Medical University of Lublin, Aleje Racławickie 1, 20-059 Lublin
   https://orcid.org/0009-0006-9946-8448
   adaw357@gmail.com
10. Weronika Salasa [WS]
    Stefan Wyszynski Specialist Hospital in Lublin, Krasnicka 100, 20-718 Lublin
    https://orcid.org/0000-0002-8683-2582
    weronikasal@gmail.com

Abstract:

Introduction

Creatine, a supplement popular especially among athletes, is gaining increasive attention from scientists worldwide due to its potential health benefits, among other things, in the context of its anti-cancer application.

Materials and methods

The following review of studies is based on scientific articles from recent years available in the PubMed and Google Scholar databases. Key search terms included: "creatine", "creatine supplementation", "creatine in sports", "supplementation in sports", "creatine in cancer".

Results

The literature review unequivocally demonstrates the beneficial impact of creatine supplementation on numerous health and athletic aspects. Creatine has been observed to have a positive effect on selected aspects of cancer treatment, such as reducing tumor mass, complementing the action of commonly used anticancer drugs, and slowing down the wasting associated with cancer diseases.

Conclusion

The promising results of the cited studies indicate that further research into creatine supplementation and its mechanisms of action is necessary. There is a need for further research on the positive impact of creatine supplementation in the treatment of cancer diseases. The significant potential of creatine supplementation may enable its inclusion in clinical practice in the future and the development of an effective therapeutic strategy based on it in the treatment of cancer diseases.

Key words: "creatine"; "creatine supplementation"; "creatine in sports"; "supplementation in sports"; "creatine in cancer".

Introduction

Creatine (Cr) and its phosphorylated form - phosphocreatine (PCr) are important sources of energy in the form of adenosine triphosphate (ATP) for cells with high energy demands, such as skeletal muscles and cardiac muscle. [1][3] Creatine was discovered in 1832 as a natural component of skeletal muscles, while research into its use as a food additive began in 1912. [2] Creatine, also known as methylguanidinoacetic acid, is naturally synthesized in the body from three amino acids: arginine, glycine, and methionine, through reactions occurring in the kidneys (with the involvement of arginine:glycine amidinotransferase - AGAT) and the liver (with the involvement of guanidinoacetic acid methyltransferase - GAMT). [3][4][8] Additionally, humans obtain creatine from a diet rich in red meat and seafood. [3][4] In the cytoplasm of target cells, the enzyme creatine kinase (CK) enables the phosphorylation of creatine into its high-energy form - phosphocreatine. The highest concentration of creatine and phosphocreatine is observed in skeletal muscles - they contain up to 95% of the creatine found in the human body. High concentrations are also observed in cardiac muscle and the testicles.

[4] Approximately one-third of creatine is stored in the free form, while about two-thirds are stored as phosphocreatine. [7][8] The daily production of creatine in the human body is estimated to be around 1 - 2 g. [5] It is worth noting that approximately 1-2% of creatine in muscles undergoes non-enzymatic breakdown to creatinine. [4]

I. Supplementation - available forms of creatine and dosage

There are various forms of creatine available, such as creatine citrate, creatine serum, creatine ethyl ester, creatine nitrate and creatine monohydrate.The most effective form of creatine supplementation is the use of creatine monohydrate, which has been available since the 1990s. The highest concentration of creatine in the serum is observed approximately one hour after oral supplementation. [4] The most common approach to creatine supplementation involves one of two schemes. In both schemes, the initial phase involves loading. The first scheme involves starting supplementation with high doses of creatine, typically around 20 - 25 g, or 0.3 g/kg of body weight of creatine per day for 5 - 7 days, while the second scheme entails supplementation of 3-5 g of creatine for about a month. After the loading phase, which results in an increase in muscle creatine stores, comes the maintenance phase, during which supplementation ranges from 0.07 g/kg of body weight to 5 g of creatine per day. [1][5][6] It's worth noting that consuming creatine in combination with carbohydrates more effectively increases creatine concentration in muscles than when consuming creatine alone. [1] Furthermore, individuals with low levels of stored muscle creatine, such as vegetarians, tend to exhibit a better response to supplementation. [9]

II. The popularity of creatine

In surveys among athletes and military personnel, it has been estimated that 15 - 40% of respondents use creatine, with men engaged in strength sports more frequently using it. [4] Creatine is readily available, does not require a prescription, and is not a banned substance by anti-doping committees (including WADA) and the International Olympic Committee (IOC). [6] Additionally, creatine is recognized as a safe ingredient by the U.S. Food and Drug Administration (FDA). [2] In the following review, we will focus on the impact of creatine supplementation on sports performance, muscle strength, brain function, and its potential applications in oncology.

Safety: creatine supplementation and kidney function

Some authors have suggested that creatine supplementation may lead to a deterioration in kidney function in healthy individuals, but this theory has been debunked based on numerous studies. [4] Such theories may stem from the fact that 1-2% of creatine and phosphocreatine contained in muscles is broken down into creatinine. [4][10] Another reason for such allegations

against creatine is the fact that it may cause water retention in the human body. It is an osmotically active substance, and at the beginning of supplementation - using a loading phase scheme of approximately 20 g of creatine per day for 5 - 7 days - water retention in the body can indeed be observed. However, in observations lasting 5 - 10 weeks, no increase in total body water has been observed. [10]

Lugaresi et al. conducted a randomized, double-blind study on a group of 26 young resistance-trained men following a high-protein diet, where the results of two groups were analyzed. The first group consisted of 12 individuals taking creatine, while the second group comprised 14 individuals who did not take creatine (placebo). After 12 weeks of conducting the study, parameters allowing assessment of kidney function were evaluated, such as: creatinine clearance, serum creatinine, albuminuria, proteinuria, sodium and potassium levels in blood and urine. Between the studied groups, no significant differences were found in any of the above parameters ($p > 0.05$). [11]

In another study conducted by de Oliveira Vilar Neto et al., 30 young men (students) who were not taking creatine were divided into 3 groups. The first group was the placebo group, the second group of participants took 3 g of creatine per day, and the third group took 5 g of creatine per day. Before starting creatine supplementation and after a period of 35 days, the results of renal parameters were compared. When comparing individual groups, no significant differences were found in parameters such as serum creatinine, eGFR and other kidney biomarkers ($p > 0.05$). Pairwise analysis revealed that in the group where participants supplemented with creatine, there was a significant decrease in eGFR and an elevated level of serum creatinine ($p < 0.05$). However, these values still fall within the normal range, and the elevated values compared to the baseline level can be explained by the fact that creatinine is a by-product of creatine metabolism. [12]

Williamson et al. made an interesting observation. In a study involving a physically active 42-year-old man, supplementation with creatine resulted in an elevated level of creatinine, which normalized after discontinuation of the supplement. The patient did not present any symptoms of kidney disease, kidney function, and blood pressure remained within normal ranges. This demonstrates that there is a possibility where creatine supplementation can lead to a misinterpretation in kidney function tests, suggesting that the patient is suffering from acute kidney failure. In this case, it is also caused by the fact that creatine and phosphocreatine undergo non-enzymatic breakdown to creatinine, which is transported to the kidneys and excreted in urine. However, this does not indicate a deterioration in kidney function or kidney disease. [13] The level of creatinine can be increased by consuming meat or creatine, so in such

cases, kidney assessment is recommended based on tests that do not rely on creatinine levels in urine or serum. [14]

Creatine Supplementation in Sports

Creatine monohydrate is the most common supplement used by athletes. [4][15] A beneficial effect of creatine on training adaptation is observed in many sports disciplines. [1][3] According to the International Society of Sports Nutrition (ISSN), creatine monohydrate is the most effective available ergogenic supplement for increasing high-intensity exercise performance. [4] The beneficial effects of creatine are observed in relation to many parameters of the human body, both in men and women, in young, adult, and elderly individuals. [16] Creatine supplementation allows athletes to significantly increase training volume and improve performance, especially during single high-intensity sets and intermittent anaerobic exercises, but its impact on endurance exercises is not fully understood. [1][16]

I. The impact of creatine on muscle strength

In the study by Mills et al., the researchers investigated the impact of creatine supplementation on muscle mass and strength outcomes in young active adults. The researchers divided 22 participants into 2 groups: a group taking creatine and a placebo group. Selected parameters were evaluated after 6 weeks of resistance training, with 5 training sessions recorded each week. In both groups, a similar increase in body mass and muscle thickness was observed. However, in the group supplemented with creatine, a significant increase in strength in bench press, leg press, and overall strength ($p < 0.05$) was additionally observed, with no significant changes noted in the placebo group. [17]

Significant differences can also be observed in the group of advanced athletes. Zajac et al. conducted a study on the effect of creatine supplementation on repeated sprint ability test (RAST) in a group of 16 well-trained male soccer players. Participants were divided into 3 groups: a group receiving 5.5 g of magnesium creatine chelate, a placebo group and a control group. The study lasted for a total of 16 weeks. After this period, the results were summarized, showing a significant increase in strength parameters: average power and max power, as well as a significant improvement in time (decrease in total time) (all parameters $p < 0.05$) in the anaerobic sprint test. It is worth noting that in the supplementation group, a higher concentration of creatinine was observed compared to the other groups, but it remained within normal limits. [18]

Even in a shorter period of creatine supplementation, a positive impact on muscle strength can be observed. In the study conducted by Atakan et al., which involved 30 female futsal players, the impact of creatine supplementation for a period of 7 days on leg muscle

strength, speed, and agility was examined. Significant improvement in all these parameters ($p < 0.05$) was observed in the group supplementing with creatine compared to the placebo group. Furthermore, no significant differences were observed in body weight measurements ($p > 0.05$). [19]

II. The impact of creatine on lean body mass

Creatine supplementation supports fat loss and enables the maintenance of muscle mass, which combined with physical activity, can effectively aid in combating obesity. [3][20] Pinto C. et al. investigated the effects of creatine supplementation on selected body parameters in an older non-exercising group of individuals aged between 60 and 80 years. 27 participants were divided into 2 groups: one group supplemented with creatine monohydrate at a dose of 5 g per day and the other group received a placebo. All participants took part in a 12-week resistance training program, with 3 training sessions per week. After this period, it was observed that muscle strength increased in both groups, as did body mass, but there were no significant differences in either group ($p > 0.05$). However, a significant increase in muscle mass, a significant increase in lean body mass, a tendency to reduce fat tissue, and a significant decrease in gynoid and android fat tissue were observed in the creatine supplementation group compared to the placebo group ($p < 0.05$ in each of these parameters). [21]

III. The impact of creatine on post-training recovery

Creatine has antioxidant and anti-inflammatory effects, leading to faster ATP regeneration and influencing glycogen resynthesis, among other effects. Therefore, its supplementation enables acceleration of post-exercise recovery. [1] This can be observed in the study conducted by Wang et al. on a group of 30 university athletes, divided into a creatine supplementation group and a placebo group, examining the impact of creatine supplementation on muscle damage and athletic performance. After 4 weeks of training, based on selected parameters, it was noticed that creatine supplementation reduces muscle damage in complex training, as evidenced by the reduction of muscle damage biomarkers in the creatine supplementation group compared to the placebo group. [22]

Creatine supplementation and brain function

In addition to skeletal muscles, another organ where we observe high concentrations of creatine is the human brain. [23] Creatine supplementation leads to an increase in the amount of creatine in the human brain by 5 - 15% [4], which is facilitated by the ability to cross the blood-brain barrier. [23] Furthermore, unlike muscles, the brain is capable of synthesizing creatine. [24] It has been proven that creatine can improve cognitive functions and memory

parameters, especially in older individuals. [23][25] Additionally, creatine supplementation enables an increase in brain bioenergetics and has neuroprotective effects in conditions associated with cerebral ischemia. [4]

Creatine supplementation in cancer therapy - its potential applications

Malignant tumors are one of the leading causes of death worldwide. [29] Scientists are seeking new effective methods of treatment in oncology. Research is being conducted to search for substances that may aid in the fight against cancerous diseases. One of these substances is creatine. In this part of the study, we will focus on harnessing the well-known properties of creatine, including those mentioned above, for its potential impact on cancer treatment.

I. The impact on T lymphocytes and tumor growth limitation.

As we have already observed, creatine and phosphocreatine enable the provision of energy to cells in the form of ATP. In some types of tumors, we observe low energy availability and low creatine content in T lymphocytes, which are responsible for the immune response in cancerous diseases. This is one of the areas where creatine supplementation can be explored for potential applications. [3]

In the study by Di Base et al., the focus was precisely on the role of T lymphocytes in the immune response against melanoma cells and colon cancer. In the conducted study on a group of mice administered with creatine, a significant inhibition of tumor growth was observed. T lymphocytes require large amounts of energy for their functioning, which they compete for with cancer cells. It has been observed that creatine effectively enables anti-cancer T lymphocytes to replenish their energy reserves, thereby allowing them to effectively perform their function. [26]

In another study, a beneficial effect of creatine supplementation on limiting the growth of the tumor was also observed. The study was conducted on 50 Wistar Walker 256 rats tumor-bearing, which were divided into a group receiving creatine supplementation and a placebo group. After 15 days of supplementation, it was observed that in the group receiving creatine, there was a reduction in tumor growth by as much as 30% ($p = 0.03$) compared to the placebo group. Despite this significant difference, no difference was observed in the survival rate ($p = 0.65$). [27]

II. Impact on pharmacotherapy with anticancer drugs.

Pal et al. focused on other potential benefits of creatine supplementation in cancer therapy. An experiment was conducted to investigate the effect of methylglyoxal (MB) on cancer cells. The experiment was conducted on tumor-bearing mice. One group received only methylglyoxal, while the other group received methylglyoxal along with creatine and ascorbic

acid. After 10 days of pharmacotherapy, the group receiving additional creatine showed greater regression in tumor size and longer survival compared to the group receiving only methylglyoxal. This shows that creatine supplementation can complement anticancer drug therapy just as effectively. [28]

III. Impact on muscle function, body mass and cancer cachexia

In cancer patients, weight loss is often observed, which negatively affects treatment, quality of life, and mortality among oncology patients. Weight loss is accompanied by the loss of muscle mass and muscle strength as well as fat tissue. Such cachexia is observed in 50-80% of cancer patients. Proper nutritional intervention is crucial for improving therapeutic outcomes and quality of life. [29][31]

Currently, there is no established effective treatment regimen for cancer-related cachexia, which necessitates the need to find new methods of treatment. Creatine helps strengthen muscles and improve strength, which is why it has potential applications in the treatment of cancer-related cachexia. [31]

Even in older studies, attempts have been made to utilize the properties of creatine, which allow healthy individuals to, among other things, increase muscle mass. Norman et al. conducted research on the impact of creatine supplementation on chemotherapy-treated patients with colorectal cancer. The study involved 31 participants, who were divided into a group receiving creatine supplementation (16 individuals) and a placebo group (15 individuals). Selected muscle function parameters were observed for a period of 8 weeks. The results showed that among the group of colorectal cancer patients treated with chemotherapy, there was no improvement in muscle function, body mass, or quality of life as assessed by the QLQ30 questionnaire. [29]

In the study conducted by Jatoi et al., terminally ill cancer patients in the experimental group were orally administered creatine at a dose of 5 g for 5 days, followed by 2 g per day. The study involved 263 individuals, with 134 receiving creatine and 129 receiving a placebo. After one month of the study, only 3 individuals gained 10% or more body weight, including 2 individuals receiving creatine and 1 from the control group. Appetite of the participants was also assessed using a questionnaire, and no significant differences were noted between the two groups.

Another assessed parameter was grip strength and bioelectrical impedance. In this case, no significant differences were observed between the two groups. [30]

However, promising results were found in the study conducted by Wei et al. using a mouse model of cancer cachexia. Eighteen mice were divided into 3 groups: the first without

cachexia, the second with cachexia, and the third with cachexia supplemented with creatine. A range of measurable parameters was assessed. In the group supplemented with creatine, a protective effect of creatine against cancer-induced cachexia was observed compared to the cachectic group that did not receive creatine supplementation. Creatine supplementation resulted in slower weight loss, protection of the muscle groups from atrophy, increased grip strength of the limbs, and increased lean body mass. Additionally, an increase in body weight without tumor growth was observed, and most importantly, a decrease in tumor mass. [31]

Conclusions

The above study provides information about the impact of creatine supplementation on the human body. Creatine is a very popular supplement widely used, especially by athletes. The positive effects of its supplementation can be observed by both women and men, as well as by individuals of all ages, including young, adults, and elderly individuals, and both experienced athletes and non-athletes. Among the best-documented benefits of creatine supplementation is its positive impact on skeletal muscle strength and post-workout recovery. Additionally, it has a beneficial effect on increasing lean body mass without increasing overall body weight. There is also observed beneficial effects on cognitive function and neuroprotective properties.

There are several possible mechanisms for using creatine supplementation in cancer-related conditions. Creatine has a variety of properties: it enables energy access for T lymphocytes, thereby limiting tumor growth, and other potential effects, such as influencing anticancer pharmacotherapy and slowing down the loss of body mass associated with cancer. Continuing research on creatine supplementation in cancer treatment, analyzing and investigating the mechanisms of its potential application, is essential.

Author's contribution

Conceptualization, Wojciech Mądry, Aleksandra Mazurkiewicz and Justyna Marcicka; methodology, Joanna Męczyńska; software, Nazarii Saiuk; check, Joanna Męczyńska, Tomasz Seredyński and Michał Andrzej Kozicz; formal analysis, Magdalena Kołodziej and Adriana Wojciechowska; investigation, Adriana Wojciechowska and Weronika Salasa; resources, Magdalena Kołodziej; data curation, Justyna Marcicka; writing - rough preparation, Wojciech Mądry; writing - review and editing, Aleksandra Mazurkiewicz and Nazarii Saiuk; visualization, Michał Andrzej Kozicz; supervision, Tomasz Seredyński; project administration, Joanna Męczyńska; receiving funding, Weronika Salasa

All authors have read and agreed with the published version of the manuscript.

Funding statement

The study did not receive special funding.

Informed Consent Statement

Not Applicable.

Acknowledgments

Not Applicable.

Conflict of Interest Statement

The Authors Report No Conflict Of Interest.

References:

1. Forbes SC, Candow DG, Neto JHF, Kennedy MD, Forbes JL, Machado M, Bustillo E, Gomez-Lopez J, Zapata A, Antonio J. Creatine supplementation and endurance performance: surges and sprints to win the race. J Int Soc Sports Nutr. 2023 Dec;20(1):2204071.
   Available from: https://doi.org/10.1080/15502783.2023.2204071
2. Sergej M. Ostojic, Creatine as a food supplement for the general population, Journal of Functional Foods, Volume 83, 2021, 104568.
   Available from: https://doi.org/10.1016/j.jff.2021.104568
3. Kreider RB, Stout JR. Creatine in Health and Disease. Nutrients. 2021 Jan 29;13(2):447.
   Available from: https://doi.org/10.3390/nu13020447
4. Kreider RB, Kalman DS, Antonio J, Ziegenfuss TN, Wildman R, Collins R, Candow DG, Kleiner SM, Almada AL, Lopez HL. International Society of Sports Nutrition position stand: safety and efficacy of creatine supplementation in exercise, sport, and medicine. J Int Soc Sports Nutr. 2017 Jun 13;14:18.
   Available from: https://doi.org/10.1186/s12970-017-0173-z
5. Andres S, Ziegenhagen R, Trefflich I, Pevny S, Schultrich K, Braun H, Schänzer W, Hirsch-Ernst KI, Schäfer B, Lampen A. Creatine and creatine forms intended for sports nutrition. Mol Nutr Food Res. 2017 Jun;61(6).
   Available from: https://doi.org/10.1002/mnfr.201600772
6. Butts J, Jacobs B, Silvis M. Creatine Use in Sports. Sports Health. 2018 Jan/Feb;10(1):31-34.
   Available from:: https://doi.org/10.1177/1941738117737248
7. Ribeiro, F.; Longobardi, I.; Perim, P.; Duarte, B.; Ferreira, P.; Gualano, B.; Roschel, H.; Saunders, B. Timing of Creatine Supplementation around Exercise: A Real Concern?

Nutrients 2021, 13, 2844. Available from: https://doi.org/10.3390/nu13082844

8. Wu G. Important roles of dietary taurine, creatine, carnosine, anserine and 4-hydroxyproline in human nutrition and health. Amino Acids. 2020 Mar;52(3):329-360. Available from: https://doi.org/10.1007/s00726-020-02823-6
9. Chilibeck PD, Kaviani M, Candow DG, Zello GA. Effect of creatine supplementation during resistance training on lean tissue mass and muscular strength in older adults: a meta-analysis. Open Access J Sports Med. 2017 Nov 2;8:213-226. Available from: https://doi.org/10.2147/OAJSM.S123529
10. Antonio J, Candow DG, Forbes SC, Gualano B, Jagim AR, Kreider RB, Rawson ES, Smith-Ryan AE, VanDusseldorp TA, Willoughby DS, Ziegenfuss TN. Common questions and misconceptions about creatine supplementation: what does the scientific evidence really show? J Int Soc Sports Nutr. 2021 Feb 8;18(1):13. Available from: https://doi.org/10.1186/s12970-021-00412-w
11. Lugaresi R, Leme M, de Salles Painelli V, Murai IH, Roschel H, Sapienza MT, Lancha Junior AH, Gualano B. Does long-term creatine supplementation impair kidney function in resistance-trained individuals consuming a high-protein diet? J Int Soc Sports Nutr. 2013 May 16;10(1):26. Available from: https://doi.org/10.1186/1550-2783-10-26
12. de Oliveira Vilar Neto J, da Silva CA, Meneses GC, Pinto DV, Brito LC, da Cruz Fonseca SG, de Sousa Alves R, Martins AMC, de Oliveira Assumpção C, De Francesco Daher E. Novel renal biomarkers show that creatine supplementation is safe: a double-blind, placebo-controlled randomized clinical trial. Toxicol Res (Camb). 2020 May 13;9(3):263-270. Available from: https://doi.org/10.1093/toxres/tfaa028
13. Williamson L, New D. How the use of creatine supplements can elevate serum creatinine in the absence of underlying kidney pathology. BMJ Case Rep. 2014 Sep 19;2014:bcr2014204754. Available from: https://doi.org/10.1136/bcr-2014-204754
14. Holeček M. Side effects of amino acid supplements. Physiol Res. 2022 Mar 25;71(1):29-45. Available from: https://doi.org/10.33549/physiolres.934790

15. Balestrino M. Role of Creatine in the Heart: Health and Disease. Nutrients. 2021 Apr 7;13(4):1215.
Available from: https://doi.org/10.3390/nu13041215
16. Wax B, Kerksick CM, Jagim AR, Mayo JJ, Lyons BC, Kreider RB. Creatine for Exercise and Sports Performance, with Recovery Considerations for Healthy Populations. Nutrients. 2021 Jun 2;13(6):1915.
Available from: https://doi.org/10.3390/nu13061915
17. Mills S, Candow DG, Forbes SC, Neary JP, Ormsbee MJ, Antonio J. Effects of Creatine Supplementation during Resistance Training Sessions in Physically Active Young Adults. Nutrients. 2020 Jun 24;12(6):1880.
Available from: https://doi.org/10.3390/nu12061880
18. 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.
Available from: https://doi.org/10.3390/nu12102961
19. M.M. Atakan, M.B. Karavelioğlu, H. Harmancı, M. Cook, S. Bulut, Short term creatine loading without weight gain improves sprint, agility and leg strength performance in female futsal players, Science & Sports, Volume 34, Issue 5, 2019, Pages 321-327, ISSN 0765-1597.
Available from: https://doi.org/10.1016/j.scispo.2018.11.003
20. Forbes SC, Candow DG, Krentz JR, Roberts MD, Young KC. Changes in Fat Mass Following Creatine Supplementation and Resistance Training in Adults ≥50 Years of Age: A Meta-Analysis. J Funct Morphol Kinesiol. 2019 Aug 23;4(3):62.
Available from:https://doi.org/10.3390/jfmk4030062
21. Pinto, C. L., Botelho, P. B., Carneiro, J. A., and Mota, J. F. (2016) Impact of creatine supplementation in combination with resistance training on lean mass in the elderly. Journal of Cachexia, Sarcopenia and Muscle, 7: 413–421.
Available from: https://doi.org/10.1002/jcsm.12094
22. Wang, C.-C.; Fang, C.-C.; Lee, Y.-H.; Yang, M.-T.; Chan, K.-H. Effects of 4-Week Creatine Supplementation Combined with Complex Training on Muscle Damage and Sport Performance. Nutrients 2018, 10, 1640.
Available from: https://doi.org/10.3390/nu10111640
23. Forbes SC, Cordingley DM, Cornish SM, Gualano B, Roschel H, Ostojic SM, Rawson ES, Roy BD, Prokopidis K, Giannos P, Candow DG. Effects of Creatine Supplementation on

Brain Function and Health. Nutrients. 2022 Feb 22;14(5):921. Available from: https://doi.org/10.3390/nu14050921

24. Roschel H, Gualano B, Ostojic SM, Rawson ES. Creatine Supplementation and Brain Health. Nutrients. 2021 Feb 10;13(2):586. Available from: https://doi.org/10.3390/nu13020586

25. Prokopidis K, Giannos P, Triantafyllidis KK, Kechagias KS, Forbes SC, Candow DG. Effects of creatine supplementation on memory in healthy individuals: a systematic review and meta-analysis of randomized controlled trials. Nutr Rev. 2023 Mar 10;81(4):416-427. Available from: https://doi.org/10.1093/nutrit/nuac064

26. Di Biase S, Ma X, Wang X, Yu J, Wang YC, Smith DJ, Zhou Y, Li Z, Kim YJ, Clarke N, To A, Yang L. Creatine uptake regulates CD8 T cell antitumor immunity. J Exp Med. 2019 Dec 2;216(12):2869-2882. Available from: https://doi.org/10.1084/jem.20182044

27. Campos-Ferraz PL, Gualano B, das Neves W, Andrade IT, Hangai I, Pereira RT, Bezerra RN, Deminice R, Seelaender M, Lancha AH. Exploratory studies of the potential anti-cancer effects of creatine. Amino Acids. 2016 Aug;48(8):1993-2001. Available from: https://doi.org/10.1007/s00726-016-2180-9

28. Pal A, Roy A, Ray M. Creatine supplementation with methylglyoxal: a potent therapy for cancer in experimental models. Amino Acids. 2016 Aug;48(8):2003-13. Available from: https://doi.org/10.1007/s00726-016-2224-1

29. Victoria-Montesinos D, García-Muñoz AM, Navarro-Marroco J, Lucas-Abellán C, Mercader-Ros MT, Serrano-Martínez A, Abellán-Aynés O, Barcina-Pérez P, Hernández-Sánchez P. Phase Angle, Handgrip Strength, and Other Indicators of Nutritional Status in Cancer Patients Undergoing Different Nutritional Strategies: A Systematic Review and Meta-Analysis. Nutrients. 2023 Apr 6;15(7):1790. Available from: https://doi.org/10.3390/nu15071790

30. Jatoi A, Steen PD, Atherton PJ, Moore DF, Rowland KM, Le-Lindqwister NA, Adonizio CS, Jaslowski AJ, Sloan J, Loprinzi C. A double-blind, placebo-controlled randomized trial of creatine for the cancer anorexia/weight loss syndrome (N02C4): an Alliance trial. Ann Oncol. 2017 Aug 1;28(8):1957-1963. Available from: https://doi.org/10.1093/annonc/mdx232

31. Wei L, Wang R, Lin K, Jin X, Li L, Wazir J, Pu W, Lian P, Lu R, Song S, Zhao Q, Li J, Wang H. Creatine modulates cellular energy metabolism and protects against cancer

cachexia-associated muscle wasting. Front Pharmacol. 2022 Dec 7;13:1086662. Available from: https://doi.org/10.3389/fphar.2022.1086662