REVIEW ARTICLE

Creatine beyond muscle metabolism: Changing constant of human body

Yuriy Boretsky. *Department of Biochemistry and Hygiene. Ivan Boberskyi Lviv State University of Physical Culture. Lviv, Ukraine.*
Iryna Hlozhyk. *Department of Biochemistry and Hygiene. Ivan Boberskyi Lviv State University of Physical Culture. Lviv, Ukraine.*
Vira Hashchyshyn. *Department of Biochemistry and Hygiene. Ivan Boberskyi Lviv State University of Physical Culture. Lviv, Ukraine.*
Nataliia Paraniak. *Department of Biochemistry and Hygiene. Ivan Boberskyi Lviv State University of Physical Culture. Lviv, Ukraine.*
Roksolana Tymochko-Voloshyn. *Department of Biochemistry and Hygiene. Ivan Boberskyi Lviv State University of Physical Culture. Lviv, Ukraine.*
Vitaliy Ivashchenko. *Department of Traumatology, Orthopedics and Military Field Surgery. Danylo Halytsky Lviv National Medical University. Lviv Regional Hospital of War Veterans and Repressed People Named After Yu. Lypa. Lviv, Ukraine.*
Volodymyr Boretsky. *Medical Laboratory «MeDiS». Lviv, Ukraine.*
Yaroslav Svyshch ✉ **.** *Department of Athletics. Ivan Boberskyi Lviv State University of Physical Culture. Lviv, Ukraine.*

ABSTRACT

Creatine plays a vital role in the normal metabolism of the central nervous system, heart, bones, and muscle tissues. It is one of the most extensively used dietary supplements worldwide. Creatine plays a critical role in energy metabolism, functioning as a source of high-energy phosphate groups that facilitate the fast recycling of ADP into ATP within cells, particularly during stressed states. The biosynthesis of creatine requires the essential substrates arginine and S-adenosylmethionine, which can influence the regulation of metabolism in the human body. Creatine acts as a negative regulator of its own synthesis and transport. The daily creatine dose can reach 0.4 g/kg of body weight. Although the absorption rate of high doses of creatine is 20-40%, they help enhance physical performance and athletic results. Despite the long history of creatine research and widespread use of creatine in sports, the precise molecular mechanisms governing its metabolism, excretion, and the functioning of the phosphocreatine energy buffer remain to be studied in detail. This review analyses the recent research on the impact of creatine supplements on health and athletic performance and the molecular mechanisms of its regulation within the human body.

Keywords: Creatine metabolism regulation, Human health, Physical performance, Creatinine clearance.

Cite this article as:
Boretsky, Y., Hlozhyk, I., Hashchyshyn, V., Paraniak, N., Tymochko-Voloshyn, R., Ivashchenko, V., Boretsky, V., & Svyshch, Y. (2025). Creatine beyond muscle metabolism: Changing constant of human body. *Journal of Human Sport and Exercise, 20*(2), 715-730. https://doi.org/10.55860/jynq3v03

✉ **Corresponding author.** *Department of Athletics, Ivan Boberskyi Lviv State University of Physical Culture 11 Kostiushka Str., Lviv, 79000, Ukraine.*
E-mail: yaroslavsvyshch@ldufk.edu.ua

Submitted for publication January 29, 2025.
Accepted for publication March 07, 2025.
Published March 26, 2025.
Journal of Human Sport and Exercise. ISSN 1988-5202.

doi: https://doi.org/10.55860/jynq3v03

INTRODUCTION

Creatine (after the Greek word for meat, κρέας "*kreas*", methylguanidoacetic acid, $(H_2N)(HN)CN(CH_3)CH_2CO_2H$) was originally isolated by Chevreul from skeletal muscles in 1832. The majority of creatine (about 90%) in the human body is accumulated in skeletal muscles, where the total concentration of creatine and phosphocreatine can reach up to 30 mM. In brain tissue, the content of creatine is significantly lower (up to 10mM) (Walliman et al., 1992; Wyss et al., 2007). The body's creatine reserves are maintained in two ways: by endogenous biosynthesis and through dietary intake (Bonilla et al., 2021; Wallimann & Harris, 2016; Wyss & Schulze, 2002; Wyss et al., 2007).

Creatine stimulates various physiological responses beyond its contribution to cellular energy needs. It promotes the differentiation of muscle cells and neurons and protects them from oxidative stress (Sestili et al., 2016; Wallimann et al., 2011). Mutations in the genes encoding the enzyme of creatine biosynthesis and/or its transporter cause psycho-neurological disorders that compromise speaking ability and motor skills. These results further indicate the importance of creatine in human health (Cheillan et al., 2012). In healthy individuals, creatine intake improves the time to react to choices and psychological balance and reduces mental fatigue (Candow et al., 2023; Watanabe et al., 2002). Creatine dietary supplements support normal heart function and bone tissue mineralization (Balestrino, 2021; Forbes et al., 2022).

In most cases, using creatine dietary supplements provides increased anaerobic buffering capacity and reduces protein breakdown, resulting in increased muscle mass and physical performance (Twycross-Lewis et al., 2016). Consuming large amounts of creatine in doses higher than recommended can cause nausea, vomiting, diarrhoea, and acne. These adverse effects disappear quickly after properly adjusting creatine consumption (Ostojic & Ahmetovic, 2008). If the recommended doses are exceeded, most of the creatine consumed is excreted from the body within a day. The mechanisms and regulation of creatine excretion require further study.

Creatine and its phosphorylated form are relatively unstable and degrade to creatinine at a rate of about 2% per day (Wyss & Kaddurah-Daouk, 2000). Creatinine is excreted from the body by the kidneys through organic ion transporters. The levels of creatinine in blood serum and urine depend on many factors. Despite that, the average amount of creatine and creatinine in the body is relatively constant for each individual (Chernozub et al., 2020). In several studies, this indicator has been used to evaluate the content of other marker compounds in the body (Hall & Trojian, 2013; Oosterwijk, 2022).

Creatine is one of the most widely used ergogenic aids for athletes (Bonilla et al., 2021; Harris et al., 1992). Creatine is also increasingly used as a dietary supplement by other population groups, significantly increasing its production and sales (Bredahl et al., 2021). The purpose of this review is to provide an up-to-date summary and discussion of the current body of research focusing on: (1) the regulation of creatine metabolism, (2) the role of creatine in human health, (3) use of creatine as a dietary and bioactive supplement.

METHODS

This review was completed using a narrative, non-systematic approach. The search for papers was conducted using the following databases: PubMed, Cochrane, ScienceDirect, EBSCO-host from 2000 to 2024. The search was performed using the following keywords and their combinations: creatine, creatine biosynthesis regulation, creatine transport, creatine supplementation, human health, sport performance, resistance training, muscle damage, training adaptation, creatinine clearance. Articles were chosen for

inclusion based on the information they outlined and with a specific focus on creatine biosynthesis regulation, creatine transport, creatine supplementation, human health. Further citations were found, evaluated, and incorporated. Thus, in some instances, several articles beyond the period mentioned above were included.

DISCUSSION

Creatine biosynthesis and transport

The first reaction in creatine biosynthesis, the transfer of the amidino group of L-arginine to the N-amine group of L-glycine, is catalysed by L-arginine-glycine amidinotransferase (AGAT) (EC 2.1.4.1) (Tormanen, 1990; McGuire et al., 1984). This is the rate-limiting step in this biosynthetic pathway. In this reaction, L-arginine formed within the kidney is used as a donor of the amidino group (Wyss, 2000). Although arginine is formed de novo in humans, these synthetic pathways do not provide sufficient arginine quantities. Thus, humans do have dietary needs of it. It should be noted that arginine serves not only as a building block of proteins but also as an essential substrate for the synthesis of nitric oxide, an effector of MTOR and focal adhesion kinase cell signalling pathways. Lack of arginine can compromise immunity, anti-oxidative responses, wound healing etc. The products of the first reaction in creatine biosynthesis are L-ornithine and guanidinoacetate. It is believed that in the human body, most guanidinoacetate is synthesized in the kidneys. Two forms of L-arginine: glycine amidinotransferase have been identified in kidney cells: cytosolic and mitochondrial, both encoded by the GATM gene (Humm et al., 1997). N-guanidinoacetate is transported through the blood to the liver, where it is methylated. S-adenosylmethionine (SAM) is used as the methyl group donor. About 40% of S-adenosylmethionine synthesized is thought to be spent on creatine biosynthesis (Brosnan et al., 2011). The synthesis of S-adenosylmethionine, the transfer of the adenosyl group from ATP to methionine, is catalysed by methionine adenosyltransferase (EC 2.5.1.6). Methionine adenosyltransferase exists in three forms that differ by subunit composition (mains are encoded by the human genes MAT1A and MAT2A), tissue expression and kinetic properties (Chamberlin et al., 2000). It is hard to overstate the importance of S-adenosylmethionine balance for human metabolism. This compound is used as the sole source of the methyl group in most methylation reactions, including creatine biosynthesis, whereas its metabolites, S-adenosylhomocysteine and homocysteine, can provoke various diseases. The methyl group from S-adenosylmethionine is transferred to guanidinoacetate at the final step of creatine biosynthesis, catalysed by guanidinoacetate-N-methyltransferase (GAMT) (EC 2.1.1.2) (Joncquel-Chevalier Curt et al., 2015). Thus, the biosynthesis of creatine requires two potentially deficient substrates, arginine and S-adenosylmethionine, whereas a decrease in their content can influence the regulation of human body metabolism. Someone could speculate that substantial amounts of both arginine and S-adenosylmethionine are stored for cellular needs under creatine supplementation conditions.

Synthesized creatine is distributed through the blood to body tissues and absorbed according to their needs. The creatine absorption is facilitated by a high-affinity transporter CRT-1 (gene SLC6A8). The properties of this transporter have been well studied and described in numerous works and reviews (Ferrada et al., 2024; Salomons et al., 2003, Tropak et al., 2023). The human SLC6A12 gene encodes another potential creatine transporter. A mutation in this gene, found in patients with cataracts, significantly reduces creatine transport. In rats lacking the SLC6A12 homolog, elevated creatine concentrations have been observed in urine (Abplanalp et al., 2013). Possibly, the potential creatine transporter encoded by the SLC6A12 gene is not expressed in the cells of the central nervous system (Bhatt et al., 2023). This is indirectly supported by studies on the role of the main creatine transporter (CRT-1) and mutations in its gene SLC6A8 that cause psycho-neurological disorders (Ferrada et al., 2024). The involvement of both transporters in the excretion of creatine and creatinine should be investigated, especially in persons who use creatine dietary supplements.

Although creatine biosynthesis in homeothermic species has been explored for a long time, questions regarding the regulation of this pathway, the involvement of different cells and tissues in its synthesis, and their ability to transport creatine have to be studied in detail (Barcelos et al., 2016; Carducci et al., 2012; Yan & Bu, 2024).

Phosphocreatine as an energy buffer

The involvement of phosphocreatine in energy metabolism has been extensively studied using muscle cells as a model. During the initial seconds of physical exertion, when the level of ADP in myocytes rises significantly, phosphocreatine is used for fast regeneration of ATP (Bessman & Carpenter, 1985; Wallimann & Harris, 2016). The transfer of phosphate groups from phosphocreatine to ADP is catalysed by creatine kinase present in myofibrils (MM-CK) (Bessman & Carpenter, 1985; Guimarães-Ferreira, 2014; Zhao et al., 2007). The products of this reaction are creatine and ATP, which is used again as an energy source for muscle contraction. Creatine and orthophosphate formed in the myofibrils diffuse back to the mitochondria. In mitochondria, the ATP level is very high, whereas the levels of phosphocreatine and ADP are low. This balance favours the phosphorylation of creatine using the energy from ATP. The reaction is catalysed by creatine kinases located in the mitochondrial intermembrane space (Bonilla et al., 2021; Echegaray & Rivera, 2001; Qin et al., 1999; Wallimann & Harris, 2016). It should be noted that one of them, namely umtCK creatine kinase, interacts with the inner membrane ATP transporter and the outer membrane anion transporter VDAC (voltage-dependent anion carrier), facilitating the rapid transfer of phosphocreatine from the mitochondria to the cytosol (Wallimann & Harris, 2016).

The products of this reaction are phosphorylated creatine and ADP. The formed phosphocreatine diffuses back from mitochondria to myofibrils, where ADP is phosphorylated to ATP again. Thus, mitochondrial aerobic metabolism is the primary source of energy that is transferred to creatine by means of phosphorylation. Then, this high-energy phosphate group is transferred on ADP, rapidly restoring ATP concentration in the myofibrils. This energy supply mechanism, known as the "*phosphocreatine shuttle*" serves as an effective "*energy buffer*" for muscle tissue (Bessman & Carpenter, 1985; Bonilla et al., 2021; Miotto & Holloway, 2016; Wallimann & Harris, 2016).

A plausible explanation for such a complex transfer of high-energy bonds is that the phosphocreatine molecule is significantly smaller and diffuses faster than the relatively large ATP molecule (Balestrino, 2021). This ensures the relative stability of ATP concentration, which is the most essential and indispensable effector of the regulation of metabolisms. The capacity and efficiency of this energy supply mechanism depend on the creatine concentration in muscles, the intensity of mitochondrial aerobic metabolism (oxidative phosphorylation), and the balance of creatine kinases activity. Similar mechanisms have been found to operate in the cells of the nervous and immune systems (Saito et al., 2022; Schlattner et al., 2016).

Four creatine kinase genes have been identified in the human genome. The CKMT1B gene, encoding mitochondrial (ubiquitous) creatine kinase umtCK, is located on chromosome 15 (15q15.3) in the sequence with coordinates 15:43300001-44500000. The CKMT2 gene, encoding muscle sarcomeric mitochondrial creatine kinase smtCK, is located on chromosome 5 (5q14.1) in the sequence with coordinates 5:81201341-81301565. The CKM gene, encoding muscle cytosolic creatine kinase CK-MM, is located on chromosome 19 (19q13.32) in the sequence with coordinates 45306413-45322875. The CKB gene, encoding brain cytosolic creatine kinase BB-CK, is located on chromosome 14 (14q32.33) in the sequence with coordinates 14:103519667-103522833 (https://www.ebi.ac.uk/gwas/genes/CKB). Several nucleotide substitutions (polymorphisms) were identified in the human genes encoding creatine kinases. Some of them are very rare (frequency less than 0.5%), which may indicate their impact in the development of pathologies

(https://www.ebi.ac.uk/gwas/). A search for information in the PubMed database revealed contradictory results regarding the impact of creatine kinase gene polymorphisms on the development of motor skills (Chen et al., 2017; Echegaray & Rivera, 2001; Ginevičienė et al., 2021). More data are required to verify such possible influence of the genetic background.

Regulation of creatine metabolism

Using human haploid cells (HAP1) as a model, it was found that the amount of AGAT protein fused with a reporter protein is regulated in response to creatine concentrations in the incubation medium. Authors speculated that there is a specific mechanism of creatine-dependent transcriptional regulation of this pathway, as proposed in the rat model (McGuire et al., 1984; Tropak et al., 2023). Similar patterns have been observed in studies of the mouse brain: a decrease in creatine availability caused an increase in the expression of the creatine transporter gene (Jensen et al., 2020). Based on the comparative analysis of these studies, one can suggest that in homeothermic species, the expression of genes involved in creatine biosynthesis and transport increases significantly during creatine deficiency. Thus, creatine is a negative effector of its own biosynthesis and transport. Most likely, this mechanism is of particular importance for the proper balance of S-adenosylmethionine and arginine, the key substances in the metabolism of methyl groups and nitric oxide, respectively.

Interestingly, the use of creatine precursor guanidinoacetate as a dietary supplement caused a significant increase in creatine concentration in the blood of healthy individuals (Ostojic et al., 2013; Ostojic, 2022; Schulze, 2003; Stockler-Ipsiroglu & van Karnebeek, 2014). These findings indirectly suggest that guanidinoacetate may be involved in mechanisms activating the second reaction of creatine synthesis. Possibly such a mechanism evolved evolutionary to avoid cytotoxicity of guanidinoacetate. In addition, the activity of the creatine transporter is regulated by AMP-activated protein kinase via the mTOR pathway, reflecting a possible influence on energy metabolism (Li et al., 2010). Although these hypotheses can explain the substantial impact of exogenous creatine on physical performance, they must be studied in detail.

At least two types of post-translational modifications were reported to regulate the activity of muscle cytosolic creatine kinase (M-CK), namely modifications of a cysteine residue and phosphorylation. M-CK loses enzymatic activity when a cysteine residue (Cys283) is chemically modified or when an intermolecular disulfide bond is formed (Hurne et al., 2000; Montasell et al., 2022). Additionally, the oxidized form of the enzyme cannot interact with myomesin, a protein of the M-line in the sarcomere. The formation of a disulfide bond between two subunits (oxidized form of the enzyme - O-CK) leads to reduced enzyme stability. Unlike the reduced form (R-CK), the oxidized form of the enzyme undergoes rapid degradation (Peris-Moreno et al., 2020; Zhao et al., 2007). Thus, the oxidation of this creatine kinase blocks the utilization of creatine phosphate for rapid ATP resynthesis in myofibrils.

Using hibernating animals as a model it was found that non-phosphorylated muscle creatine kinase exhibits higher activity than the phosphorylated form of the enzyme (Abnous & Storey, 2007). A similar regulatory mechanism was reported in the cardiac muscle of rats, where M-CK is phosphorylated by protein kinase C. Phosphorylation of M-CK shifts the equilibrium of the reaction toward the synthesis of creatine phosphate. In contrast, dephosphorylation of the enzyme shifts the equilibrium of the reaction toward the resynthesis of ATP from ADP (Lin et al., 2009). The obtained results indirectly suggest that the respiratory activity of the tissue, i.e. ATP/ADP/AMP ratio may influence the mechanisms of ATP resynthesis by regulating the activity of creatine kinases (Peris-Moreno et al., 2020; Reddy et al., 2000). Nevertheless, phosphocreatine decreases the sensitivity of mitochondrial respiration to ADP, whereas creatine has the opposite effect. During transition from rest to high intensity exercise, decrease in the phosphocreatine/creatine ratio will effectively increase

the sensitivity of mitochondrial respiration to ADP (Walsh et al., 2001). One can suggest that there could be mutual interdependence between ATP/ADP and phosphocreatine/creatine ratios that could serve as an additional mechanism of fast respiration regulation in tight accordance to organisms needs. Obviously, this hypothesis provides some sufficient details to our understanding of molecular basis of a proper regulation of respiration, but it has to be verified experimentally.

Thus, various mechanisms are involved in regulating creatine phosphate metabolism, responding to the concentration of creatine in cells, the cell's current energy needs, and respiratory activity. Although most experiments were done on animal models, it can be assumed that very similar mechanisms of regulation of creatine metabolism function in the human body.

Using creatine to enhance sports performance

Creatine supplementation is one of the most efficient and useful ergogenic aids for athletes, which has been used since the early twentieth century. Its production and use both rose dramatically during the last decade of the twentieth century (Harris et al., 1992). Endogenous synthesis of creatine provides about half of the daily needs (Brosnan & Brosnan, 2016). The remaining part of the necessary creatine is obtained from animal-derived food products. Vegetarians who have creatine levels in tissues lower by 20–30% are recommended to consume 2–3g/day of creatine to maintain its physiological level (Kreider & Stout, 2021).

Results of molecular genetic studies of psycho-neurological disorders caused by creatine deficiency emphasize the importance of creatine metabolism for human health. Inherited creatine deficiency compromises speaking ability and motor skills and can cause progressive epilepsy and/or autism spectrum disorders (Cheillan et al., 2012). These disorders are caused by mutations in human genes involved in creatine biosynthesis or transport (Cheillan et al., 2012; Haghighatfard et al., 2023). Creatine supplementation (8g/day for 5days) increases oxygen consumption in the brain and reduces mental fatigue during repetitive mathematical calculations in healthy individuals (Watanabe, 2002). Administration of significantly higher doses (20g/day for 7days) improves time to react to choices and psychological balance (McMorris et al., 2006). Therefore, creatine supplementation positively affects the central nervous system, particularly under conditions of fatigue (Candow et al., 2023).

The creatine metabolism is essential for the normal functioning of the heart. Apparently, the phosphocreatine "*energy shuttle*" is extremely important for the proper functioning of the myocardium. It is suggested that healthy subjects will benefit from creatine supplementation, but such benefit could not be confirmed by in vivo human heart studies (Balestrino, 2021). During heart failure, levels of both creatine and phosphocreatine in cardiomyocytes decrease. It can be speculated that phosphocreatine is better retained by cardiomyocytes than creatine, as observed for the glucose-phosphoglucose pair in hepatic cells. This suggestion remains to be checked experimentally.

There are some contradictions in published data concerning the impact of creatine supplementation on the mineralization and metabolism of bone tissue (Forbes et al., 2018; Forbes et al., 2022). Possibly the reason for such inconsistency is differences in doses and approaches of creatine supplementation. In addition, it has been found that doses of creatine and the method of its consumption are important factors influencing the metabolism of bone cells – osteoblasts and osteoclasts (Zhu et al., 2023). In cell culture models, adding creatine to the cultural medium has been shown to enhance metabolic activity and differentiation of osteoblasts (Gerber et al., 2005). However, it was suggested that activation of the phosphocreatine energy buffer in osteoclasts led to an activation of bone tissue resorption processes (Zhu et al., 2023). The results of these studies indicate that creatine metabolism and the functioning of the phosphocreatine energy buffer

are both essential for bone tissue synthesis and resorption (Forbes et al., 2022; Gerber et al., 2005; Zhu et al., 2023).

Creatine is recommended as an ergogenic aid in strength sports and for athletes who endure regular maximal loads (e.g., American football, soccer, basketball, tennis, etc.) (Kreider et al., 2017). In addition to its positive impact on physical performance, creatine supplementations improve psychological balance and time to react to choice (McMorris et al., 2006). In most cases, using creatine as a dietary supplement leads to an increase in energy buffer capacity and muscle mass growth that results in enhanced physical performance (Twycross-Lewis et al., 2016). However, in some studies, no positive effect of creatine supplements on physical performance was observed (Armentano et al., 2007). This inconsistency may be explained by individual differences in the maximal creatine contents in the body (Hall & Trojian, 2013). In approximately 30 % of individuals, primarily those with creatine levels close to 150 mmol/kg of dry muscle, creatine supplements proved ineffective or only slightly effective. At the same time, in individuals with an initial creatine content of less than 110 mmol/kg of dry muscle, significant performance increases were observed with creatine supplementation (Greenhaff et al., 1993; Harris et al., 1992).

The mechanisms of the positive effects of exogenous creatine are not understood well. The observed ergogenic effects could be explained by an increased content both of in creatine and its phosphorylated form in muscles or by a decrease content of AMP breakdown products in muscles. According to this hypothesis, the primary role of phosphocreatine is to prevent the accumulation of ADP and AMP, as well as their metabolic products, inosine monophosphate and hypoxanthine. In favour of this hypothesis, creatine dependent reduction of muscle inosine monophosphate content was observed (McConell et al., 2005). Later it was reported that creatine supplementation causes decrease of hypoxanthine and uric acid in plasma (Tang et al., 2014). Creatine also can stimulate the healing of muscular microtears caused by physical loads, thereby improving muscle growth and maintenance (Bredahl et al., 2021; Hashchyshyn et al., 2022). It is important to note that high dosages of exogenous creatine can completely block its biosynthesis in the human body (Peters et al., 2015). Thus, creatine supplementation could improve the balance of arginine and S-adenosylmethionine, which is currently used as an antidepressant. The impact of these mechanisms on the overall ergogenic effect of creatine has to be studied in detail.

Table 1. Creatine supplementation recommended in different sports.

№	Dosage/Duration	Sport activity	Citation
1.	30 g/day X 7 days	Soccer	Ostojic, 2004.
2.	20-30g/day X 6-7 days + 5g/day X 63 days	Soccer	Mielgo-Ayuso et al., 2019.
3.	(~20 g/day) 0.3 g/kg of body weight X 6 days + ~2 g/day X 28 days	Tennis	Pluim et al., 2006.
4.	(~30 g/day) 0.35 g/kg of body weight X 7 days	Sprint running	Delecluse et al., 2003.
5.	20 g/day X 1-4 days 10 g/day X 5-6 days 5 g/day X 7-28 days	Volleyball	Lamontagne-Lacasse et al., 2011.
6.	(~3 g/day) 0.04 g/kg of body weight X 70 days	Rowing	Fernández-Landa et al., 2020.
7.	(~20 g/day) 0.3 g/kg of body weight X 5 days	Ice-hockey	Cornish et al., 2006.
8	~5 g/day 0.3 g/ X 4 days	Swimming	Theodorou et al., 2005.
9.	4 g/day X 42 days	Taekwondo	Manjarrez-Montes de Oca et al., 2013.
10.	20 g/day X 5-7 days	Weightlifting Powerlifting	Kreider, 2003.

Based on the studies by Harris et al. (1992), it was recommended to take 20 grams of creatine monohydrate per day for 5-10 days, achieving a 25-30% increase in muscle creatine levels. Table 1 presents several

different approaches, but there are many more protocols for creatine supplementation (Wax et al., 2021). Depending on the type of sport, consuming 3-30 grams per day of creatine as supplements to sports cocktails is recommended. Plasma concentration of creatine typically reaches its maximum approximately 60 minutes after oral ingestion of creatine monohydrate (Hultman et al., 1996; Kreider et al., 2017). After muscles creatine stores are fully saturated, it is recommended to consume 3-5 grams of creatine per day to keep them. However, some studies suggest that in some instances, dosages of 5-10 grams per day may be necessary (Hall & Trojian, 2013; Harris et al., 1992; Hultman et al., 1996; Greenhaff et al., 1994; Kreider, 2003). The alternative dosing protocol involves taking 3 grams per day of creatine monohydrate over 28 days (Hultman et al., 1996).

The use of the metabolic precursor of creatine, guanidinoacetic acid, to increase creatine levels in the body was reported earlier. It was found that oral administration of guanidino acetic acid is an effective aid to increase creatine content in muscles (Ostojic, 2022; Ostojic et al., 2013; Schulze, 2003; Stockler-Ipsiroglu & van Karnebeek, 2014). Obtained results could indicate a possible role of guanidinoacetic acid as a positive effector of creatine biosynthesis. However, this approach may cause severe issues due to the toxicity of guanidinoacetic acid and increased homocysteine levels in plasma. The latter is a risk factor in cardiovascular disease development (Peters et al., 2015). Disturbance of methyl group transfer and elevated homocysteine levels are thought to be both a cause and a consequence of metabolic syndrome (Ulloque-Badaracco et al., 2023). That can lead to disturbances in eating behaviour and changes in the human microbiome, resulting in decreased performance and athletic achievement (Lind et al., 2018; Radziejewska et al., 2020). So, such an approach is not currently recommended.

While creatine is a relatively safe supplement, it can cause a few adverse effects when overdosed. The most common side effect is temporary weight gain due to water retention. It is known that creatine causes moderate water retention and reduces diuresis, especially during the loading phase. Increased intracellular water volume increases the risk of developing compartment syndrome and muscle spasms (Butts et al., 2018; Kim et al., 2015). Creatine supplementations also could lead to both liver and kidney function disturbances. Other digestive tract disturbances, such as nausea, vomiting, diarrhoea, and acne, may occur (Ostojic & Ahmetovic, 2008). To reduce these, it is recommended to fortify creatine-containing sports cocktails with optimal proportions of vitamins B6, B9, B12, and betaine (Selhub, 1999; Ulloque-Badaracco et al., 2023). Adverse effects caused by creatine overdose quickly disappear after creatine consumption is appropriately reduced.

In most cases, using recommended creatine supplements significantly increases its content in muscles. However, simple calculations based on published data indicate that the absorption rate is less than 40%, whereas experimental data suggest that about half of the consumed creatine is excreted in urine within 24 hours (Burke et al., 2001). It is possible that creatine could diffuse into the intestines, where it might degrade under the influence of the gut microbiota (Wyss & Kaddurah-Daouk, 2000).

Excretion of creatinine from the body

Creatine and its phosphorylated form are somewhat unstable. They irreversibly degrade to creatinine. The degradation rate is approximately 2% per day (Wyss & Kaddurah-Daouk, 2000). Apparently, creatinine has no biological function and is excreted by the kidneys. Organic cation transporter (OCT2) had been shown to play a key role in the active excretion of creatinine (Ciarimboli et al., 2012; Lepist et al., 2014; Shen et al., 2015). Recently, it was suggested that some other transporters (namely organic anion transporter (OAT2), multidrug and toxin extrusion pump (MATE1/2K)) could also be involved in creatinine extrusion (Mathialagan et al., 2024; Mathialagan et al., 2021). One can assume that these transporters are involved in creatine

excretion, too. That can explain the high excretion of creatine into the urine when creatine monohydrate is used as a supplement. Besides, creatinine can diffuse into the intestines, where it could undergo further degradation by bacterial enzymes (Zakalskiy et al., 2020; Wyss & Kaddurah-Daouk, 2000).

The creatinine concentration in plasma is used in routine medical practice to determine the glomerular filtration rate, an integral indicator of a kidney excretory function. The normal creatinine levels in blood for women is 44-97μM, whereas for men – 62-115μM. Decreased creatinine concentration is observed with insufficient meat consumption (for instance, vegetarian diets, fasting) and during the first and second trimesters of pregnancy. Hypercreatininemia can be associated with kidney pathology, including conditions caused by medications (such as contrast agents for X-rays, aminoglycoside antibiotics, cephalosporin antibiotics, statins, etc.). When only one kidney is functioning, the creatinine level in blood typically increases to 159-168μM. Elevated serum creatinine concentration (above 177μM and 885μM for children and adults correspondingly) indicates renal insufficiency (Banfi et al., 2012). Dehydration, muscle damage, and consumption of large amounts of creatine as a dietary supplement can cause significantly increased creatinine content in blood and urine (Samra & Abcar, 2012).

In healthy individuals, the levels of creatinine in serum and urine are characteristic indicators for each person, depending on total muscle mass, fitness level, individual genetic traits, daily water intake, etc. (Chernozub et al., 2020; Karakukcu, 2024; Oosterwijk, 2022). This observation allows for assessing adaptive changes in training processes and the detailed analysis of changes in other biochemical markers during adaptation to physical exertion.

CONCLUSIONS

Creatine is a widely used ergogenic aid among athletes. In most cases, it has been shown that supplementing with creatine can significantly improve an individual's ability to adapt to intense physical exertion and enhance athletic performance. The effectiveness of creatine supplementation can vary considerably among individuals, and this variation can be attributed to individual genetic characteristics. These characteristics determine the efficiency of creatine absorption and accumulation. Understanding these genetic factors is crucial because it can help explain why creatine supplementation is more effective for some individuals than others. The role of the potential creatine transporter SLC6A12 in the processes of its absorption and excretion requires further investigation. The inconsistent results of recent studies on the impact of creatine kinases genes polymorphisms on the development and manifestation of motor skills illustrate the complexity of the subject and underline the need for further investigation. Consuming excessive amounts of creatine can suppress its own biosynthesis, increasing the levels of arginine and S-adenosylmethionine, with concomitant positive physiological effects. Creatine is regarded as one of the positive effectors in the regulation of myoblast proliferation and differentiation. The importance of these effects of creatine in adaption to physical load requires further investigation. However, it should be noted that the type and frequency of physical exertion affect the level of creatine accumulation. Possibly, there is a close interrelationship between the regulation of the phosphocreatine buffer's functioning and the intensity of respiration. Future studies may provide insight into the mechanisms that regulate creatine homeostasis in the human body.

AUTHOR CONTRIBUTIONS

Conceptualization, Yuriy Boretsky and Yaroslav Svyshch; data analysis: Nataliia Paraniak, Roksolana Tymochko-Voloshyn, Vitaliy Ivashchenko, Volodymyr Boretsky; formal analysis: Vira Hashchyshyn and Yaroslav Svyshch; original draft preparation: Yuriy Boretsky, Iryna Hlozhyk, Vira Hashchyshyn, Nataliia

Paraniak, Roksolana Tymochko-Voloshyn, Vitaliy Ivashchenko, Volodymyr Boretsky, Yaroslav Svyshch; review and editing: Yuriy Boretsky, Iryna Hlozhyk, Vira Hashchyshyn; supervision: Yuriy Boretsky and Yaroslav Svyshch.

SUPPORTING AGENCIES

No funding agencies were reported by the authors.

DISCLOSURE STATEMENT

No potential conflict of interest was reported by the authors.

REFERENCES

Abnous, K., & Storey, K. B. (2007) Regulation of skeletal muscle creatine kinase from a hibernating mammal. Arch. Biochem. Biophys, 467(1), 10-19. https://doi.org/10.1016/j.abb.2007.07.025

Abplanalp, J., Laczko, E., Philp, N. J., Neidhardt, J., Zuercher, J., Braun, P., Schorderet, D.F., Munier, F.L., Verrey, F., Berger, W., Camargo, S.M., Kloeckener-Gruissem, B. (2013). The cataract and glucosuria associated monocarboxylate transporter MCT12 is a new creatine transporter. Hum Mol Genet, 22(16), 3218-26. https://doi.org/10.1093/hmg/ddt175

Armentano, M. J., Brenner, A. K., Hedman, T. L., Solomon, Z. T., Chavez, J., Kemper, G. B., Salzberg, D., Battafarano, D. F., Christie, D. S. (2007). The effect and safety of short-term creatine supplementation on performance of push-ups. Mil Med, 172(3), 312-7. https://doi.org/10.7205/MILMED.172.3.312

Balestrino, M. (2021). Role of Creatine in the Heart: Health and Disease. Nutrients, 13(4), 1215. https://doi.org/10.3390/nu13041215

Banfi, G., Colombini, A., Lombardi, G., Lubkowska, A. (2012). Metabolic markers in sports medicine. Adv Clin Chem, 56, 1-54. https://doi.org/10.1016/B978-0-12-394317-0.00015-7

Barcelos, R. P., Stefanello, S. T., Mauriz, J. L., Gonzalez-Gallego, J., Soares, F. A. (2016). Creatine and the Liver: Metabolism and Possible Interactions. Mini Rev Med Chem, 16(1), 12-8. https://doi.org/10.2174/1389557515666150722102613

Bessman, S.P., & Carpenter, C. L. (1985). The Creatine-Creatine Phosphate Energy Shuttle. Annu. Rev. Biochem, 54, 831-862. https://doi.org/10.1146/annurev.bi.54.070185.004151

Bhatt, M., Gauthier-Manuel, L., Lazzarin, E., Zerlotti, R., Ziegler, C., Bazzone, A., Stockner, T., Bossi, E. (2023). A comparative review on the well-studied GAT1 and the understudied BGT-1 in the brain. Front Physiol, 14, 1145973. https://doi.org/10.3389/fphys.2023.1145973

Bonilla, D. A., Kreider, R. B., Stout, J. R., Forero, D. A., Kerksick, C. M., Roberts, M. D., Rawson, E. S. (2021). Metabolic Basis of Creatine in Health and Disease: A Bioinformatics-Assisted Review. Nutrients, 13(4), 1238. https://doi.org/10.3390/nu13041238

Bredahl, E. C., Eckerson, J. M., Tracy, S. M., McDonald, T. L., Drescher, K. M. (2021). The Role of Creatine in the Development and Activation of Immune Responses. Nutrients, 13(3), 751. https://doi.org/10.3390/nu13030751

Brosnan, J. T., da Silva, R. P., & Brosnan, M. E. (2011). The metabolic burden of creatine synthesis. Amino Acids, 40(5), 1325-31. https://doi.org/10.1007/s00726-011-0853-y

Brosnan, M. E., & Brosnan, J. T. (2016). The role of dietary creatine. Amino Acids, 48(8), 1785-91. https://doi.org/10.1007/s00726-016-2188-1

Burke, D. G., Smith-Palmer, T., Holt, L. E., Head, B., Chilibeck, P. D. (2001). The effect of 7 days of creatine supplementation on 24-hour urinary creatine excretion. J Strength Cond Res, 15(1), 59-62. https://doi.org/10.1519/00124278-200102000-00010

Butts, J., Jacobs, B., & Silvis, M. (2018). Creatine Use in Sports. Sports Health, 10(1), 31-34. https://doi.org/10.1177/1941738117737248

Candow, D. G., Forbes, S. C., Ostojic, S. M., Prokopidis, K., Stock, M. S., Harmon, K. K., Faulkner, P. (2023). "Heads Up" for Creatine Supplementation and its Potential Applications for Brain Health and Function. Sports Med, 53(1), 49-65. https://doi.org/10.1007/s40279-023-01888-z

Carducci, C., Carducci, C., Santagata, S., Adriano, E., Artiola, C., Thellung, S., Gatta, E., Robello, M., Florio, T., Antonozzi, I., Leuzzi, V., Balestrino, M. (2012). In vitro study of uptake and synthesis of creatine and its precursors by cerebellar granule cells and astrocytes suggests some hypotheses on the physiopathology of the inherited disorders of creatine metabolism. BMC Neurosci, 13, 41. https://doi.org/10.1186/1471-2202-13-41

Chamberlin, M. E., Ubagai, T., Mudd, S. H., Thomas, J., Pao, V. Y., Nguyen, T. K., Levy, H. L., Greene, C., Freehauf, C., Chou, J. Y. (2000). Methionine adenosyltransferase I/III deficiency: novel mutations and clinical variations. Am J Hum Genet, 66(2), 347-55. https://doi.org/10.1086/302752

Cheillan, D., Joncquel-Chevalier, C. M., Briand, G., Salomons, G. S., Mention-Mulliez, K., Dobbelaere, D., … Vamecq, J. (2012). Screening for primary creatine deficiencies in French patients with unexplained neurological symptoms. Orphanet J Rare Dis, 7, 96. https://doi.org/10.1186/1750-1172-7-96

Chen, C., Sun, Y., Liang, H., Yu, D., Hu, S. (2017). A meta-analysis of the association of CKM gene rs8111989 polymorphism with sport performance. Biol Sport, 34(4), 323-330. https://doi.org/10.5114/biolsport.2017.69819

Chernozub, A., Potop, V., Korobeynikov, G., Timnea, O. C., Dubachinskiy, O., Ikkert, O., Briskin, Y., Boretsky, Y., Korobeynikova, L. (2020). Creatinine is a biochemical marker for assessing how untrained people adapt to fitness training loads. PeerJ, 8, e9137. https://doi.org/10.7717/peerj.9137

Ciarimboli, G., Lancaster, C. S., Schlatter, E., Franke, R. M., Sprowl, J. A., Pavenstädt, H., Massmann, V., Guckel, D., Mathijssen, R. H., Yang, W., Pui, C. H., Relling, M. V., Herrmann, E., Sparreboom, A. (2012). Proximal tubular secretion of creatinine by organic cation transporter OCT2 in cancer patients. Clin Cancer Res, 18(4), 1101-8. https://doi.org/10.1158/1078-0432.CCR-11-2503

Cornish, S. M., Chilibeck, P. D., & Burke, D. G. (2006). The effect of creatine monohydrate supplementation on sprint skating in ice-hockey players. J Sports Med Phys Fitness, 46(1), 90-8. PMID: 16596105.

Delecluse, C., Diels, R., & Goris, M. (2003). Effect of creatine supplementation on intermittent sprint running performance in highly trained athletes. J Strength Cond Res, 17(3), 446-54. https://doi.org/10.1519/1533-4287(2003)017<0446:EOCSOI>2.0.CO;2

Echegaray, M., & Rivera, M.A. (2001). Role of creatine kinase isoenzymes on muscular and cardiorespiratory endurance: genetic and molecular evidence. Sports Med, 31(13), 919-34. https://doi.org/10.2165/00007256-200131130-00003

Fernández-Landa, J., Fernández-Lázaro, D., Calleja-González, J., Caballero-García, A., Córdova Martínez, A., León-Guereño, P., Mielgo-Ayuso, J. (2020). Effect of Ten Weeks of Creatine Monohydrate Plus HMB Supplementation on Athletic Performance Tests in Elite Male Endurance Athletes. Nutrients, 12(1), 193. https://doi.org/10.3390/nu12010193

Ferrada, E., Wiedmer, T., Wang, W. A., Frommelt, F., Steurer, B., Klimek, C., Lindinger, S., Osthushenrich, T., Garofoli, A., Brocchetti, S., Bradberry, S., Huang, J., MacNamara, A., Scarabottolo, L., Ecker, G.F., Malarstig, A., Superti-Furga, G. (2024). Experimental and Computational Analysis of Newly Identified Pathogenic Mutations in the Creatine Transporter SLC6A8. J Mol Biol, 436(2), 168383. https://doi.org/10.1016/j.jmb.2023.168383

Forbes, S. C., Chilibeck, P. D., & Candow, D. G. (2018). Creatine Supplementation During Resistance Training Does Not Lead to Greater Bone Mineral Density in Older Humans: A Brief Meta-Analysis. Front Nutr, 5, 27. https://doi.org/10.3389/fnut.2018.00027

Forbes, S. C., Ostojic, S. M., Souza-Junior, T. P., Candow, D. G. (2022). A High Dose of Creatine Combined with Resistance Training Appears to Be Required to Augment Indices of Bone Health in Older Adults. Ann Nutr Metab, 78(3), 183-186. https://doi.org/10.1159/000520967

Gerber, I., ap Gwynn, I., Alini, M., Wallimann, T. (2005). Stimulatory effects of creatine on metabolic activity, differentiation and mineralization of primary osteoblast-like cells in monolayer and micromass cell cultures. Eur Cell Mater, 10, 8-22. https://doi.org/10.22203/eCM.v010a02

Ginevičienė, V., Jakaitienė, A., Utkus, A., Hall, E. C. R, Semenova, E. A., Andryushchenko, L. B., Larin, A. K., Moreland, E., Generozov, E. V., Ahmetov, I. I. (2021). CKM Gene rs8111989 Polymorphism and Power Athlete Status. Genes (Basel), 12(10), 1499. https://doi.org/10.3390/genes12101499

Greenhaff, P. L., Casey, A., Short, A. H., Harris, R., Soderlund, K., Hultman, E. (1993). Influence of oral creatine supplementation of muscle torque during repeated bouts of maximal voluntary exercise in man. Clin Sci (Lond), 84(5), 565-71. https://doi.org/10.1042/cs0840565

Guimarães-Ferreira, L. (2014). Role of the phosphocreatine system on energetic homeostasis in skeletal and cardiac muscles. Einstein (Sao Paulo), 12(1), 126-31. https://doi.org/10.1590/S1679-45082014RB2741

Haghighatfard, A., Ghaderi, A. H., Mostajabi, P., Kashfi, S. S., Mohabati Somehsarayee, H., Shahrani, M., Mehrasa, M., Haghighat, S., Farhadi, M., Momayez Sefat, M., Shiryazdi, A. A., Ezzati, N., Qazvini, M. G., Alizadenik, A., Moghadam, E. R. (2023). The first genome-wide association study of internet addiction; Revealed substantial shared risk factors with neurodevelopmental psychiatric disorders. Res Dev Disabil, 133, 104393. https://doi.org/10.1016/j.ridd.2022.104393

Hall, M., & Trojian, T. H. (2013). Creatine supplementation. Curr Sports Med Rep, 12(4), 240-4. https://doi.org/10.1249/JSR.0b013e31829cdff2

Harris, R. C, Soderlund, K., & Hultman, E. (1992). Elevation of creatine in resting and exercised muscle of normal subjects by creatine supplementation. Clin Sci (Lond), 83(3), 367-374. https://doi.org/10.1042/cs0830367

Hashchyshyn, V., Tymochko-Voloshyn, R., Paraniak, N., Vovkanych, L., Hlozhyk, I., Trach, V., Muzyka, F., Serafyn, Y., Prystupa, E., Boretsky, Y. (2022). Regeneration of Skeletal Muscle Fibers and Regulation of Myosatellitocytes Metabolism. Cytol. Genet, 56, 253-260. https://doi.org/10.3103/S0095452722030033

Hultman, E., Söderlund, K., Timmons, J. A., Cederblad, G., Greenhaff, P. L. (1996). Muscle creatine loading in men. J Appl Physiol, 81(1), 232-7. https://doi.org/10.1152/jappl.1996.81.1.232

Humm, A., Fritsche, E., Steinbacher, S., Huber, R. (1997). Crystal structure and mechanism of human L-arginine:glycine amidinotransferase: a mitochondrial enzyme involved in creatine biosynthesis. EMBO J, 16(12), 3373-85. https://doi.org/10.1093/emboj/16.12.3373

Hurne, A. M., Chai, C. L., & Waring, P. (2000). Inactivation of rabbit muscle creatine kinase by reversible formation of an internal disulfide bond induced by the fungal toxin gliotoxin. J Biol Chem, 275(33), 25202-6. https://doi.org/10.1074/jbc.M002278200

Jensen, M., Müller, C., Schwedhelm, E., Arunachalam, P., Gelderblom, M., Magnus, T., Gerloff, C., Zeller, T., Choe, C. U. (2020). Homoarginine- and Creatine-Dependent Gene Regulation in Murine Brains with l-Arginine: Glycine Amidinotransferase Deficiency. Int J Mol Sci, 21(5), 1865. https://doi.org/10.3390/ijms21051865

Joncquel-Chevalier Curt, M., Voicu, P. M., Fontaine, M., Dessein, A. F., Porchet, N., Mention-Mulliez, K., Dobbelaere, D., Soto-Ares, G., Cheillan, D., Vamecq, J. (2015). Creatine biosynthesis and transport in health and disease. Biochimie, 119, 146-65. https://doi.org/10.1016/j.biochi.2015.10.022

Karakukcu, C., Kocer, D., Uzen, V., Saracoglu, H. (2024). Creatinine normalization approach to diluted urine samples screened by LC-MS/MS method. Int J Med Biochem, 7(2), 95-100. https://doi.org/10.14744/ijmb.2024.57441

Kim, J., Lee, J., Kim, S., Yoon, D., Kim, J., Sung, D. J. (2015). Role of creatine supplementation in exercise-induced muscle damage: a mini review. J Exerc Rehabil, 11, 244-250. https://doi.org/10.12965/jer.150237

Kreider, R. B. (2003). Effects of creatine supplementation on performance and training adaptations. Mol Cell Biochem, 244(1-2), 89-94. https://doi.org/10.1023/A:1022465203458

Kreider, R. B., & Stout, J. R. (2021). Creatine in Health and Disease. Nutrients, 13(2), 447. https://doi.org/10.3390/nu13020447

Kreider, R. B., Kalman, D. S., Antonio, J., Ziegenfuss, T. N., Wildman, R., Collins, R., Candow, D. G., Kleiner, S. M., Almada, A. L., Lopez, H. L. (2017). International Society of Sports Nutrition position stand: safety and efficacy of creatine supplementation in exercise, sport, and medicine. J Int Soc Sports Nutr, 14, 18. https://doi.org/10.1186/s12970-017-0173-z

Lamontagne-Lacasse, M., Nadon, R., & Goulet, E. D. B. (2011). Effect of creatine supplementation on jumping performance in elite volleyball players. Int J Sports Physiol Perform, 6(4), 525-33. https://doi.org/10.1123/ijspp.6.4.525

Lepist, E. I., Zhang, X., Hao, J., Huang, J., Kosaka, A., Birkus, G., Murray, B. P., Bannister, R., Cihlar, T., Huang, Y., Ray, A. S. (2014). Contribution of the organic anion transporter OAT2 to the renal active tubular secretion of creatinine and mechanism for serum creatinine elevations caused by cobicistat. Kidney Int, 86(2), 350-7. https://doi.org/10.1038/ki.2014.66

Li, H., Thali, R. F., Smolak, C., Gong, F., Alzamora, R., Wallimann, T., Scholz, R., Pastor-Soler, N. M., Neumann, D., Hallows, K. R. (2010) Regulation of the creatine transporter by AMP-ACTIVATED protein kinase in kidney epithelial cells. Am J Physiol Renal Physiol, 299(1), 167-177. https://doi.org/10.1152/ajprenal.00162.2010

Lin, G., Liu, Y., & MacLeod, K. M. (2009). Regulation of muscle creatine kinase by phosphorylation in normal and diabetic hearts. Cell. Mol. Life Sci, 66, 135-144. https://doi.org/10.1007/s00018-008-8575-3

Lind, M. V., Lauritzen, L., Vestergaard, H., Hansen, T., Pedersen, O., Kristensen, M., Ross, A. B. (2018). One-carbon metabolism markers are associated with cardiometabolic risk factors. Nutr Metab Cardiovasc Dis, 28(4), 402-410. https://doi.org/10.1016/j.numecd.2018.01.005

Manjarrez-Montes de Oca, R., Farfán-González, F., Camarillo-Romero, S., Tlatempa-Sotelo, P., Francisco-Argüelles, C., Kormanowski, A., González-Gallego, J., Alvear-Ordenes, I. (2013). Effects of creatine supplementation in taekwondo practitioners. Nutr Hosp, 28(2), 391-9.

Mathialagan, S., Chung, G., Pye, K., Rodrigues, A. D., Varma, M. V. S., Brown, C. (2024). Significance of Organic Anion Transporter 2 and Organic Cation Transporter 2 in Creatinine Clearance: Mechanistic Evaluation Using Freshly Prepared Human Primary Renal Proximal Tubule Cells. J Pharmacol Exp Ther, 388(1), 201-208. https://doi.org/10.1124/jpet.123.001890

Mathialagan, S., Feng, B., Rodrigues, A. D., Varma, M. V. S. (2021). Drug-Drug Interactions Involving Renal OCT2/MATE Transporters: Clinical Risk Assessment May Require Endogenous Biomarker-Informed Approach. Clin Pharmacol Ther, 110(4), 855-859. https://doi.org/10.1002/cpt.2089

McConell, G. K., Shinewell, J., Stephens, T.J., Stathis, C. G., Canny, B. J., Snow, R. J. (2005). Creatine supplementation reduces muscle inosine monophosphate during endurance exercise in humans. Med Sci Sports Exerc, 37(12), 2054-2061. https://doi.org/10.1249/01.mss.0000179096.03129.a4

McGuire, D. M., Gross, M. D., Van Pilsum, J. F., Towle, H. C. (1984). Repression of rat kidney L-arginine: glycine amidinotransferase synthesis by creatine at a pretranslational level. J Biol Chem, 259(19), 12034-8. https://doi.org/10.1016/S0021-9258(20)71316-5

McMorris, T., Harris, R. C., Swain, J., Corbett, J., Collard, K., Dyson, R. J., Dye, L., Hodgson, C., Draper, N. (2006). Effect of creatine supplementation and sleep deprivation, with mild exercise, on cognitive and psychomotor performance, mood state, and plasma concentrations of catecholamines and cortisol. Psychopharmacology, 185, 93-103. https://doi.org/10.1007/s00213-005-0269-z

Mielgo-Ayuso, J., Calleja-Gonzalez, J., Marqués-Jiménez, D., Caballero-García, A., Córdova, A., Fernández-Lázaro, D. (2019). Effects of Creatine Supplementation on Athletic Performance in Soccer Players: A Systematic Review and Meta-Analysis. Nutrients, 11(4), 757. https://doi.org/10.3390/nu11040757

Miotto, P. M., & Holloway, G. P. (2016). In the absence of phosphate shuttling, exercise reveals the in vivo importance of creatine-independent mitochondrial ADP transport. Biochem J, 473(18), 2831-43. https://doi.org/10.1042/BCJ20160373

Montasell, M. C., Monge, P., Carmali, S., Dias Loiola, L. M., Andersen, D. G., Løvschall, K. B., Søgaard, A. B., Kristensen, M. M., Pütz, J. M., Zelikin, A. N. (2022). Chemical zymogens for the protein cysteinome. Nat Commun, 13(1), 4861. https://doi.org/10.1038/s41467-022-32609-1

Oosterwijk, M. M., den Braber, N., Bakker, S. J. L., Laverman, G. D. (2022). Urinary creatinine excretion is an indicator of physical performance and function. J Cachexia Sarcopenia Muscle, 13(2), 1431-1433. https://doi.org/10.1002/jcsm.12965

Ostojic, S. M. (2004). Creatine supplementation in young soccer players. Int J Sport Nutr Exerc Metab, 14(1), 95-103. https://doi.org/10.1123/ijsnem.14.1.95

Ostojic, S. M. (2022). Guanidinoacetic Acid as a Nutritional Adjuvant to Multiple Sclerosis Therapy. Front Hum Neurosci, 16, 871535. doi: 10.3389/fnhum.2022.871535. https://doi.org/10.3389/fnhum.2022.871535

Ostojic, S. M., & Ahmetovic, Z. (2008). Gastrointestinal distress after creatine supplementation in athletes: Are side effects dose dependent? Research in Sports Medicine, 16(1), 15-22. https://doi.org/10.1080/15438620701693280

Ostojic, S. M., Niess, B., Stojanovic, M., Obrenovic, M. (2013). Creatine metabolism and safety profiles after six-week oral guanidinoacetic acid administration in healthy humans. Int J Med Sci, 10(2), 141-7. https://doi.org/10.7150/ijms.5125

Peris-Moreno, D., Taillandier, D., & Polge C. (2020). MuRF1/TRIM63, Master Regulator of Muscle Mass. Int J Mol Sci, 21(18), 6663. https://doi.org/10.3390/ijms21186663

Peters, B. A., Hall, M. N., Liu, X., Parvez, F., Siddique, A. B., Shahriar, H., Uddin, M. N., Islam, T., Ilievski, V., Graziano, J. H., Gamble, M. V. (2015). Low-Dose Creatine Supplementation Lowers Plasma Guanidinoacetate, but Not Plasma Homocysteine, in a Double-Blind, Randomized, Placebo-Controlled Trial. J Nutr, 145(10), 2245-52. https://doi.org/10.3945/jn.115.216739

Pluim, B. M., Ferrauti, A., Broekhof, F., Deutekom, M., Gotzmann, A., Kuipers, H., Weber, K. (2006). The effects of creatine supplementation on selected factors of tennis specific training. Br J Sports Med, 40(6), 507-12. https://doi.org/10.1136/bjsm.2005.022558

Qin, W., Khuchua, Z., Boero, J., Payne, R. M., Strauss, A. W. (1999). Oxidative myocytes of heart and skeletal muscle express abundant sarcomeric mitochondrial creatine kinase. Histochem J, 31(6), 357-65. https://doi.org/10.1023/A:1003748108062

Radziejewska, A., Muzsik, A., Milagro, F. I., Martínez, J. A., Chmurzynska, A. (2020). One-Carbon Metabolism and Nonalcoholic Fatty Liver Disease: The Crosstalk between Nutrients, Microbiota, and Genetics. Lifestyle Genom, 13(2), 53-63. https://doi.org/10.1159/000504602

Reddy, S., Jones, A. D., Cross, C. E., Wong, P. S., Van Der Vliet, A. (2000). Inactivation of creatine kinase by S-glutathionylation of the active-site cysteine residue. Biochem J, 347 Pt 3(Pt 3), 821-7. https://doi.org/10.1042/bj3470821

Saito, S., Cao, D. Y., Okuno, A., Li, X., Peng, Z., Kelel, M., Tsuji, N. M. (2022). Creatine supplementation enhances immunological function of neutrophils by increasing cellular adenosine triphosphate. Biosci Microbiota Food Health, 41(4), 185-194. https://doi.org/10.12938/bmfh.2022-018

Salomons, G. S., van Dooren, S. J., Verhoeven, N. M., Marsden, D., Schwartz, C., Cecil, K. M., DeGrauw, T. J., Jakobs, C. (2003). X-linked creatine transporter defect: an overview. J Inherit Metab Dis, 26(2-3), 309-18. https://doi.org/10.1023/A:1024405821638

Samra, M., & Abcar, A. C. (2012). False estimates of elevated creatinine. Perm J. Spring, 16(2), 51-2. https://doi.org/10.7812/tpp/11-121

Schlattner, U., Klaus, A., Ramirez Rios, S., Guzun, R., Kay, L., Tokarska-Schlattner, M. (2016). Cellular compartmentation of energy metabolism: creatine kinase microcompartments and recruitment of B-type creatine kinase to specific subcellular sites. Amino Acids, 48(8), 1751-74. https://doi.org/10.1007/s00726-016-2267-3

Schulze, A. (2003). Creatine deficiency syndromes. Mol Cell Biochem, 244(1-2), 143-50. https://doi.org/10.1023/A:1022443503883

Selhub, J. (1999). Homocysteine metabolism. Annu Rev Nutr, 19, 217-46. https://doi.org/10.1146/annurev.nutr.19.1.217

Sestili, P., Ambrogini, P., Barbieri, E., Sartin, S., Fimognari, C., Calcabrini, C., Diaz, A. R., Guescini, M., Polidori, E., Luchetti, F., Canonico, B., Lattanzi, D., Cuppini, R., Papa, S., Stocchi, V. (2016). New insights into the trophic and cytoprotective effects of creatine in in vitro and in vivo models of cell maturation. Amino Acids, 48(8), 1897-911. https://doi.org/10.1007/s00726-015-2161-4

Shen, H., Liu, T., Morse, B. L., Zhao, Y., Zhang, Y., Qiu, X., Chen, C., Lewin, A. C., Wang, X. T., Liu, G., Christopher, L. J., Marathe, P., Lai, Y. (2015). Characterization of Organic Anion Transporter 2 (SLC22A7): A Highly Efficient Transporter for Creatinine and Species-Dependent Renal Tubular Expression. Drug Metab Dispos, 43(7), 984-93. https://doi.org/10.1124/dmd.114.062364

Stockler-Ipsiroglu, S., & van Karnebeek, C. D. (2014). Cerebral creatine deficiencies: a group of treatable intellectual developmental disorders. Semin Neurol, 34(3), 350-6. https://doi.org/10.1055/s-0034-1386772

Tang, F. C., Chan, C. C., & Kuo, P. L. (2014). Contribution of creatine to protein homeostasis in athletes after endurance and sprint running. Eur J Nutr, 53(1), 61-71. https://doi.org/10.1007/s00394-013-0498-6

Theodorou, A. S., Havenetidis, K., Zanker, C. L., O'Hara, J. P., King, R. F., Hood, C., Paradisis, G., Cooke, C. B. (2005). Effects of acute creatine loading with or without carbohydrate on repeated bouts of maximal swimming in high-performance swimmers. J Strength Cond Res, 19(2), 265-9. https://doi.org/10.1519/15314.1

Tormanen, C. D. (1990). Comparison of the properties of purified mitochondrial and cytosolic rat kidney transamidinase. Int J Biochem, 22(11), 1243-50. https://doi.org/10.1016/0020-711X(90)90305-M

Tropak, M. B., Tkachyova, I., Gu, R., Lee, A., Schulze, A. (2023). Evidence of an intracellular creatine-sensing mechanism that modulates creatine biosynthesis via AGAT expression in human HAP1 cells. Sci Rep, 13(1), 22392. https://doi.org/10.1038/s41598-023-49860-1

Twycross-Lewis, R., Kilduff, L.P., Wang, G., Pitsiladis, Y.P. (2016). The effects of creatine supplementation on thermoregulation and physical (cognitive) performance: a review and future prospects. Amino Acids, 48(8), 1843-55. https://doi.org/10.1007/s00726-016-2237-9

Ulloque-Badaracco, J. R., Hernandez-Bustamante, E. A., Alarcon-Braga, E.A., Al-Kassab-Córdova, A., Cabrera-Guzmán, J. C., Herrera-Añazco, P., Benites-Zapata, V.A. (2023). Vitamin B12, folate, and homocysteine in metabolic syndrome: a systematic review and meta-analysis. Front Endocrinol (Lausanne), 14, 1221259. https://doi.org/10.3389/fendo.2023.1221259

Wallimann, T., & Harris, R. (2016). Creatine: a miserable life without it. Amino Acids, 48(8), 1739-50. https://doi.org/10.1007/s00726-016-2297-x

Wallimann, T., Tokarska-Schlattner, M., & Schlattner, U. (2011). The creatine kinase system and pleiotropic effects of creatine. Amino Acids, 40(5), 1271-96. https://doi.org/10.1007/s00726-011-0877-3

Wallimann, T., Wyss, M., Brdiczka, D., Nicolay, K., Eppenberger, H. M. (1992). Intracellular compartmentation, structure and function of creatine kinase isoenzymes in tissues with high and fluctuating energy demands: the 'phosphocreatine circuit' for cellular energy homeostasis. Biochem J, 281 (Pt1) (Pt 1), 21-40. https://doi.org/10.1042/bj2810021

Walsh, B., Tonkonogi, M., Söderlund, K., Hultman, E., Saks, V., Sahlin, K. (2001). The role of phosphorylcreatine and creatine in the regulation of mitochondrial respiration in human skeletal muscle. J Physiol, 537(Pt3), 971-8. https://doi.org/10.1111/j.1469-7793.2001.00971.x

Watanabe, A., Kato, N., Kato, T. (2002). Effects of creatine on mental fatigue and cerebral hemoglobin oxygenation. Neurosci Res, 42(4), 279-85. https://doi.org/10.1016/S0168-0102(02)00007-X

Wax, B., Kerksick, C. M., Jagim, A.R., Mayo, J. J., Lyons, B.C., Kreider, R. B. (2021). Creatine for Exercise and Sports Performance, with Recovery Considerations for Healthy Populations. Nutrients, 13(6), 1915. https://doi.org/10.3390/nu13061915

Wyss, M., & Kaddurah-Daouk, R. (2000). Creatine and creatinine metabolism. Physiol Rev, 80(3), 1107-213. https://doi.org/10.1152/physrev.2000.80.3.1107

Wyss, M., & Schulze, A. (2002). Health implications of creatine: can oral creatine supplementation protect against neurological and atherosclerotic disease? Neuroscience, 112(2), 243-60. https://doi.org/10.1016/S0306-4522(02)00088-X

Wyss, M., Braissant, O., Pischel, I., Salomons, G. S., Schulze, A., Stockler, S., Wallimann, T. (2007). Creatine and creatine kinase in health and disease--a bright future ahead? Subcell Biochem, 46, 309-34. https://doi.org/10.1007/978-1-4020-6486-9_16

Yan, H., & Bu, P. (2024). TAMC-derived creatine sustains glioblastoma growth. Cell Metab, 36(1), 1-3. https://doi.org/10.1016/j.cmet.2023.12.012

Zakalskiy, A. E., Stasyuk, N. Y., Zakalska, O. M., Boretsky, Y. R., Gonchar, M. V. (2020). Overexpression and one-step renaturation-purification of the tagged creatinine deiminase of Corynebacterium glutamicum in Escherichia coli cells. Cell Biol Int, 44(5), 1204-1211. https://doi.org/10.1002/cbin.11320

Zhao, T. J., Yan, Y. B., Liu, Y., Zhou, H. M. (2007). The generation of the oxidized form of creatine kinase is a negative regulation on muscle creatine kinase. J Biol Chem, 282(16), 12022-9. https://doi.org/10.1074/jbc.M610363200

Zhu, L., Tang, Y., Li, X. Y., Kerk, S. A., Lyssiotis, C. A., Feng, W., Sun, X., Hespe, G. E., Wang, Z., Stemmler, M. P., Brabletz, S., Brabletz, T., Keller, E. T., Ma, J., Cho, J. S., Yang, J., Weiss, A. (2023). Zeb1/MtCK1 metabolic axis controls osteoclast activation and skeletal remodeling. SJ.EMBO J, 42(7), e111148. https://doi.org/10.15252/embj.2022111148

