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Review on Creatine Monohydrate Enhance Muscle Growth

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Chapter-1 Introduction

Creatine monohydrate is a popular ingredient in dietary supplements, particularly sports nutrition products. Research indicates that creatine has a consistent ergogenic effect, especially with high-intensity short bursts of energy. Human data is primarily derived from acute studies involving high doses (20 g/d) with short duration, chronic studies involving lower doses (3-5 g/d) and longer duration (1 year), or a combination of both. Systematic evaluation of research designs and data does not provide a basis for risk assessment and the usual safe Upper Level of Intake (UL). The Observed Safe Level (OSL) or Highest Observed Intake (HOI) is used to determine the safety of creatine at intakes up to 5 g/d for chronic supplementation.

Creatine, first discovered in 1832, is a naturally occurring amino acid-like compound found in the liver, kidneys, and pancreas. Over 95% of the total creatine content in humans is located in skeletal muscle, with a daily turnover estimated to be around 2 g. Creatine is available as a dietary supplement in powdered (figure.1.1), tablet, and liquid forms as primarily creatine monohydrate. In the last decade, nearly 70 randomized, controlled trials have been conducted on or with creatine, with the majority examining its performance-enhancing benefits.
Initial recommendations for creatine use stemmed from early research using 5-7 days of "loading" with 20-30 g per day, resulting in increased muscle creatine content. Refinements have been made to this strategy, and now many athletes consume only one 5 g dose (figure.1.2) approximately 60 minutes prior to or immediately after training. Creatine supplementation averages a 2-5 pound greater gain in muscle mass and 5-15% greater increases in muscle strength and power compared to control or placebo subjects. Creatine supplementation does not appear to enhance endurance-related exercise performance.

Research indicates that once muscle stores of creatine are full, they can remain elevated for an additional 4-5 weeks without further supplementation. Normal healthy adults who continue to use creatine after their muscle stores have reached peak levels may find the additional creatine converted to creatinine and excreted in the urine. Urinary creatinine levels are commonly used as a marker of kidney function, and individuals who ingest creatine will frequently have elevated creatinine levels, which is normal and represents an increased rate of muscle creatine conversion to creatinine rather than an abnormality of kidney function.

The widespread use of this ingredient in dietary supplements suggests a need to evaluate the safety of creatine through quantitative risk assessment. Most upper safe levels of nutrients and related substances are based on widely applicable risk assessment models used by the US Food and Nutrition Board (FNB) in its Dietary Reference Intakes documents in 1997 and after.

Supplementing with creatine monohydrate enhances the body's total creatine and phosphocreatine reserves, which are crucial for regenerating adenosine triphosphate (ATP), the cell's primary energy source . Since its identification by Michel Eugene Chevreul in 1832, numerous peer-reviewed studies, reviews, and meta-analyses have endorsed creatine's efficacy in boosting athletic performance . Creatine monohydrate supplementation fills muscle cells with phosphocreatine and free creatine, with skeletal muscle housing approximately 95% of this content . While constantly active in energy production, the phosphagen system (also known as the ATP-creatine phosphate system [ATP-CPr/CP]) is predominantly engaged during anaerobic and/or intense exercise. Previous meta-analyses have indicated that supplementation is particularly beneficial for activities lasting under 30 seconds . The creatine kinase enzyme facilitates the transfer of the high-energy phosphate to adenosine diphosphate (ADP), converting it to ATP to meet cellular energy requirements. High-intensity exercises like sprinting and weightlifting heavily rely on the ATP-CPr system to generate muscle contractions and maintain

energy balance. This is supported by current and past research, which demonstrates that the advantages of creatine monohydrate supplementation are most evident in anaerobic activities or repeated bouts of high-intensity exercise with brief recovery intervals .

Creatine supplementation has been shown to improve physical tests, body compositions, and blood markers, including reduced inflammatory indicators and decreased lactate. It has been found to be beneficial across various age groups and training status levels, even among elite athletic populations. Creatine supplementation can increase maximal power output, anaerobic endurance, workload volume, lean mass changes, jumping performance, and sprinting performance. Across sexes, few differences have been observed in creatine supplementation, but a meta-analysis suggests that women may have higher endogenous muscle creatine compared to men. Overall, creatine supplementation has been shown to be beneficial for various sports.

Figure.1.1

figure.1.2

Literature &Review

95% of the body's creatine stores found within this muscle. It is primarily produced by the liver, kidney, and pancreas, with the endogenous production down-regulated during exogenous Creatine, a nitrogenous amine discovered in 1832, is primarily found in skeletal muscle, with creatine supplementation. The kidney synthesizes creatine from amino acids glycine and arginine, which is then transferred to the liver, where a methyl group from methionine is added, forming creatine. Circulating creatine is brought into skeletal muscle via cell membrane transporters, and the rate of creatine uptake is influenced by exercise, cathecholamines, and insulin-like growth factor.

Creatine can be phosphorylated to form phosphocreatine in a reversible enzymatic reaction facilitated by creatine kinase. The phosphate group comes from ATP forming adenosine diphosphate (ADP), while the reverse reaction occurs when ATP is being used by the cell. During short-duration, high-intensity exercises, ATP needs are met by both anaerobic glycolysis and phosphocreatine shuttle. Creatine supplementation can increase phosphocreatine stores, decrease muscle fatigue, and improve performance by prolonging the phosphocreatine shuttle.

Additionally, creatine supplementation can improve performance during exercises by faster resynthesis of phosphocreatine during rest and recovery between bouts of maximal exercise. However, conflicting data exists regarding the effectiveness of creatine supplementation in improving phosphocreatine resynthesis. Other mechanisms include aiding ATP production via glycolysis by increasing phosphofructokinase activity or buffering hydrogen ions.

Studies have shown that intramuscular stores of total creatine and phosphocreatine can be increased by supplementing with oral creatine monohydrate for 5 to 7 days with a dose of 20 to 25 g·d−1. The greatest increase is reported in the first 2 days of supplementation. The typical dosing in studies that have shown increases in strength performance includes both a loading and maintenance phase. When a carbohydrate or protein is added to creatine supplementation, there may be an increase in muscle retention of creatine , particularly in the first few days, resulting in a decreased need for loading. However, alternative dosing methods have been shown to effectively increase creatine stores and have effects on strength gains. Regimens without the creatine loading phase, 3 to 6 g·d−1 for 28 d and 6 g·d−1 for 12 wk, also have been shown to be effective in increasing creatine stores (10). The increase in creatine stores occurs more slowly and may take longer to see the strength training effects.

Creatine ethyl ester has received recent attention as one of the latest creatine variations to increase intramuscular creatine levels. Esterification of creatine decreases its hydrophilicity, allowing it to bypass the creatine transporter due to enhanced sarcolemmal permeability toward creatine. However, recent studies show that creatine ethyl ester is converted to creatinine, not creatine, and increases in plasma creatinine were found with creatine ethyl ester. Other forms of creatine, such as a buffered form of creatine, are more efficacious and/or safer to consume than creatine monohydrate.

Problem identification

The rumored idea that creatine supplementation leads to an increase in total body water (TBW) likely stems from earlier studies that indicated taking 20 g/day of creatine for six days was linked to water retention. It seems that the primary side effect experienced during the initial days of creatine use is indeed water retention. Research indicates that just three days of creatine intake led to higher TBW, extracellular body water (ECW), and intracellular water (ICW). Regrettably, the simplistic view that creatine leads to long-term water retention has become widely accepted based on these short-term responses.

Creatine acts as a substance that attracts water. Thus, when the body's creatine levels rise, it could theoretically lead to increased water retention. Creatine enters muscle cells from the bloodstream via a sodium-dependent creatine transporter. Because this transport process uses sodium, water will also be absorbed into muscle to help keep the balance of solutes inside the cells. However, due to the functioning of sodium-potassium pumps, it is unlikely that creatine supplementation significantly alters the concentration of sodium inside the cells.

Multiple studies focusing on exercise training that incorporated creatine supplementation over periods ranging from 5 to 10 weeks found no significant changes in total body water. For instance, males engaged in resistance training who consumed 0. 3 g/kg of their lean body mass in creatine daily for 7 days, followed by 0. 075 g/kg daily for four weeks, showed no notable changes in ICW, ECW, or TBW. Additionally, males who took creatine at a rate of 20 g/day for a week and then switched to 5 g/day for 21 days also displayed no significant increases in those water measurements. Similarly, both male and female participants consuming creatine at 0. 03 g/kg over six weeks noted no substantial rise in TBW. Six weeks of creatine intake by non-resistance-trained males at a dosage of 0. 3 g/kg lean body mass for five days, followed by 0. 075 g/kg for 42 days, yielded no significant alterations in TBW. In contrast, when evaluating TBW, ICW, and ECW levels before and after a month of creatine supplementation in healthy individuals, Powers et al. indicated that creatine was effective in boosting muscle creatine levels, which corresponded with an increase in body mass and TBW, but did not affect ICW or ECW volumes. In a recent study that looked at creatine supplementation alongside resistance exercise over eight weeks, Ribeiro et al. observed a notable increase of 7. 0% in TBW and 9. 2% in ICW volume compared to the placebo group, which had smaller increases. It is crucial to note that the ratio of skeletal muscle mass to ICW remained consistent in both groups. ICW plays a key role as a cellular signal for protein synthesis, thus contributing to

muscle growth over time.

To sum up, although there is some information indicating that taking creatine supplements can boost water retention, mainly due to higher intracellular volume in the short run, numerous other studies indicate that it does not change the total body water, whether intracellular or extracellular, concerning muscle mass over extended durations. Therefore, creatine supplementation might not cause water retention.

Function Kidneys are essential organs that engage in multiple important functions, playing a crucial part in keeping the body balanced. They take part in hormone-related processes, manage fluid levels, blood pressure, and electrolyte harmony; they also handle the removal of waste and harmful substances, such as toxins and medications. (figure.1)

Each kidney contains between 0. 8 and 1. 2 million tiny filtering units called nephrons. A nephron is made up of a glomerulus, which is a clump of tiny blood vessels, and a renal tubule, which includes Bowman's capsule, proximal and distal convoluted tubules, the loop of Henle, and the collecting duct. This entire structure consists of a single layer of cells that helps control the volume and concentration of urine. Initially, the blood plasma is filtered through the glomerulus into Bowman's capsule. The different parts of the renal tubule then process the filtered liquid before it is eliminated as urine. Water, electrolytes like sodium, calcium, and chloride, along with some organic substances such as glucose and amino acids, can be taken back into the bloodstream based on the body's needs. On the other hand, potassium, various

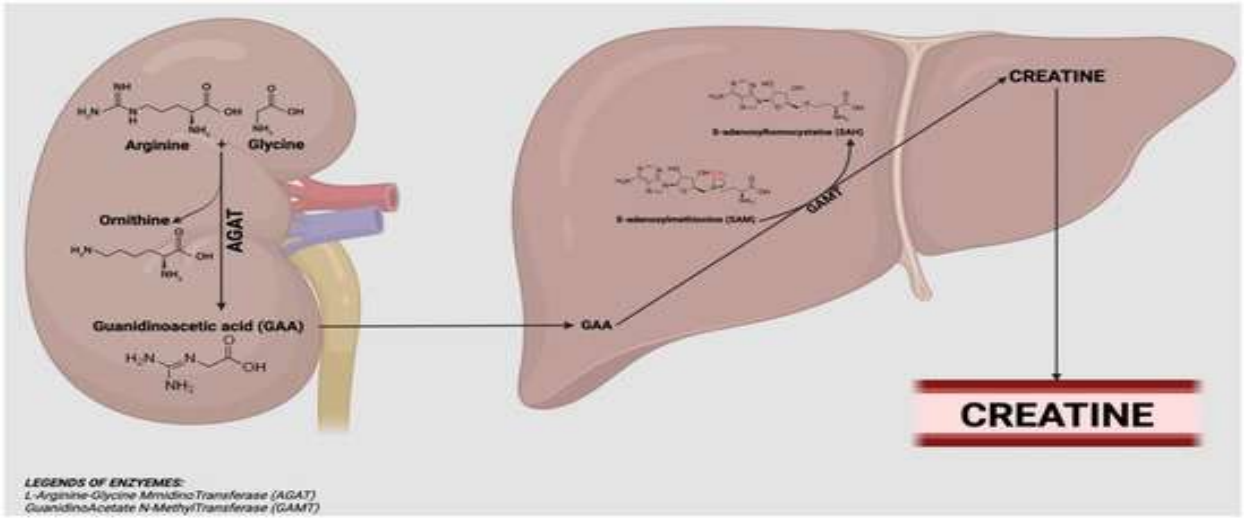

Figure .1

organic materials, and foreign compounds like penicillin are moved from the fluid outside the tubules into the renal tubule. Each of these processes is carefully managed through local or systemic control mechanisms.

Specifically, the filtration process is largely influenced by the pressure of the capillaries and the permeability of the glomerular filtration barrier, which is quite selective and relatively strong. There are three main filtration barriers fenestrated endothelial cells, the glomerular basement membrane, and special cells called podocytesthat permit most plasma elements to pass into the tubule but keep blood cells and larger proteins like albumin in the bloodstream. The presence of large molecules in the urine is a clear sign of a problem with the glomerular barrier. It is crucial to note that kidneys have a significant reserve capacity, and their function is a highly adaptable process that continuously responds to changes within the body. Research suggests that it takes the loss of at least three-quarters of kidney function before the body's balance is notably impacted.

The glomerular filtration rate, which refers to the volume of fluid that moves into Bowman's capsule each unit of time, is a key factor in assessing how well the kidneys are functioning. While it cannot be measured directly, we can estimate the glomerular filtration rate by looking at the clearance of a substance that is filtered. The most reliable technique for this evaluation involves using specific external filtration biomarkers, referred to as measured glomerular filtration rate (mGFR), which are continuously infused into the bloodstream and monitored with timed urine collections. These biomarkers, such as inulin, 99mTc-DTPA, and 51Cr-EDTA, are not produced by the body. Therefore, it is assumed that

their clearance equals the glomerular filtration rate since they pass freely through the filter but are neither reabsorbed nor secreted by the kidney tubules. Unfortunately, mGFR tests are typically only available in specialized settings, which leads to the common practice of estimating glomerular filtration rates through serum concentrations of natural biomarkers, called estimated glomerular filtration rate (eGFR), without needing direct clearance testing. For example, the levels of substances like creatinine and Cystatin C are linked to kidney health and disease progression. However, eGFR can be influenced by how quickly these biochemical markers are produced through metabolism, how the kidneys secrete or reabsorb them, and how they are eliminated. Despite significant progress in recent years, there are still many factors that can cause inaccuracies in eGFR measurements, such as smoking, inflammation, medications, hormone levels, body fat, muscle mass, and diet, which may hinder their effectiveness in accurately determining kidney function for specific populations.

This situation involves people who are using creatine supplements. Serum creatinine (Crn) is the most commonly utilized measure to evaluate kidney performance, whether on its own or as a way to estimate the glomerular filtration rate. Crn is the final product formed during creatine metabolism. Creatine breaks down naturally and permanently into Crn at a rate of around 2% of the total body reserves each day. Since long-term creatine use increases the overall creatine levels in the body, it's likely that there will be a natural spike in Crn levels in the bloodstream after taking creatine, without necessarily causing any damage to the kidneys. It's important to recognize that the opposite is also truevegetarians tend to have lower serum Crn and Crn clearance due to their limited intake of dietary creatine. Thus, the intake of creatine is a known factor that can affect Crn measurements. This is why calculations of Crn clearance that rely solely on serum Crnwithout considering its levels in urinemight not be sufficient for individuals who take creatine supplements. Ignoring this issue may result in incorrect interpretations of test outcomes and lead to wrong diagnoses, such as false positives. Furthermore, it has been proposed that taking creatine from outside sources slows down the L-arginine:glycine amidinotransferase (AGAT) reaction, which is a vital part of how the body creates its own creatine. Although this might create a balance between the intake of creatine and its breakdown, the usual doses in creatine supplementation programs generally surpass both the body's natural production and excretion rates. Additionally, reducing AGAT activity might promote the use of creatine's precursor amino acids in various metabolic processes, such as the urea cycle and the guanidine cycle. However, there is currently not enough evidence to indicate that this would lead to a notable increase in plasma and urinary urea levels in healthy people.

Methodology

The study aimed to determine the biological profile of responders and non-responders to 5-day creatine supplementation. Responders (R) increased their resting total muscle creatine concentrations by 20 mmol·kg-1 dw or greater from preload levels, while non-responders (NR) did not exceed 10 mmol·kg-1 dw of total resting Cr concentration following the 5-day supplementation phase. "Quasi responders" (QR) fell between the two criteria measures. Muscle biopsies were taken before and after the 5-day acute supplementation period to establish a biological profile of each responder subgroup.

A 2-group design was employed to determine the overall extent of creatine loading. Inferential statistics were used to determine if there was a statistically significant increase in resting cellular Cr + PCr following the 5-day acute supplementation period. The Cr supplementation group was then analyzed on an individual basis to categorize responders versus non-responders and their associated biological profile.

Eighteen recreationally weight-trained men from the Universities were recruited from the student population. Subjects had no prior history with creatine monohydrate supplementation and signed informed consent. The experiment was conducted over a 5-day loading period, with the CrS receiving 0.3 g·kg-1·d-1 following all pretest measures. The inclusion of a placebo group was to verify that a true group treatment response did occur with the proposed Cr loading protocol.

All creatine doses were measured individually using an electronically calibrated scale and dissolved in 1 L of a heated, flavored drink containing 80 g·L-1 of simple sugar. The drink was cooled to room temperature and distributed to subjects with instructions to consume the entire 1-L Cr solution in 4 equal portions throughout the day, separated by 3–4 hours. The Pl group received the flavored drink only and consumed the solution in a similar manner as the Cr S. This supplementation schedule was repeated for 5 days.

The study involved muscle biopsies from the lateral aspect of the vastus lateralis of the right leg before and after a 5-day loading period on both groups. Two tissue samples were extracted from each biopsy incision, with the first sample frozen within 3 to 5 seconds in liquid nitrogen and stored at -80°C for later biochemical analysis of Cr and PC r creatine concentrations. The second biopsy sample was oriented cross sectionally and mounted in an embedding medium (OCT) on a piece of cork, frozen in isopentane cooled to near freezing with liquid nitrogen, and stored at -80°C for later histochemical analysis.

To profile the Cr S, anthropometric measures of height, weight, and four skinfold sites (triceps, biceps, and subscapular and suprailia crest) were obtained before and after the 5-day supplementation period. Percent body fat was calculated using the formula by Durnin and Womersley.

To monitor daily fluid and protein intake, each subject completed a 3-day dietary log during three consecutive days immediately prior to and after the 5-day Cr loading period. Macronutrients, including fluid ingestion, were analyzed using a nutritional software program. Pre-post 5-day, 24-hour urine samples were collected, providing an indirect measure of water retention that might occur during the supplementation phase. A sample of the urine was also used to determine pre-post urinary Cr and Cr N concentrations using the modified reverse-phase high-performance liquid chromatography (HPLC) method of Dunnett et al. (11).

To determine upper- and lower-body strength performance changes over the 5-day Cr supplementation period, 1RM bench and incline leg press tests were performed. The testing protocol followed that outlined in Syrotuik et al. (27), which involved performing 3 submaximal warmup sets of 10, 6, and 3 repetitions with progressively higher loads. Incline leg press and bench press scores were reported to the nearest 2.5 and 1 kg, respectively.

Result and discussion

In total, 4086 publications were identified (Figure 1). These included 4049 that were excluded, and there were 37 publications available for possible inclusion (randomized controlled trials and in the last 10 years). Twenty-one studies were excluded because either the title referred to creatine kinase and not to creatine supplementation (n = 8), there was no control with a placebo (n = 5), pure creatine was not used in the studies (n = 4), no growth in the muscle was reported (n = 3), or was conducted on animals (n = 1). Besides, 16 papers were identified as being relevant for inclusion based on the description of randomized and placebo-controlled trials. The key data and findings of these studies are presented in (Table 1)

Table 1. Studies recruiting healthy untrained young subjects.

Authors (Year)	Design	QACIS Score	Participants	Creatine Dose (g/day)	Duration (Days)	Training Exercise	Evaluation Exercise	Outcome Measures (Muscle-Related)	Main Findings (Muscle-Related)
del Favero et al. [23]	RP DB	85.71	34 healthy untrained males 18–30 years old	2 × 10 g	10	N/A	Squat exercise Bench press	Muscle power output by a linear encoder 1RM	Muscle power output: Squat exercise: CR > PL (p = 0.003) Bench-press: CR > PL (p = 0.039) 1RM in CR: Post > pre Squat exercise: p = 0.027 Bench-press: p < 0.0001 No change in PL
Kavians et al. [24]	RP DB	85.71	18 healthy untrained males 23 ± 3 years old	0.07 g/kg	56	Bench press Leg press Biceps curl Tricep extension Shoulder press Lat pull-down	1RM of left exercise	Check 1RM every two weeks for eight weeks CK	1RM CR > PL within two weeks after bench, leg, and shoulder presses (p < 0.05) By six weeks, 1RM CR > PL in above three items and tricep extension (p < 0.05) Eight weeks, then same as six weeks, no significant difference in biceps curls and lat pull-downs CK, CR > PL (p ≤ 0.05)

RP: randomized parallel; DB: double blind; N/A: not applicable; RM: repetition maximum; CR: creatine; PL: placebo; CK: creatine kinase.

Conclusion

This scoping review offers a contemporary overview of existing research regarding creatine supplementation and its role in muscle growth across different groups. Creatine serves as an effective supplement for enhancing muscle strength, increasing muscle mass, and boosting athletic performance, particularly among healthy young individuals engaged in appropriate training, using various dosing methods, and participating in diverse sports activities. Nonetheless, there is a notable lack of robust, evidence-based studies examining the effectiveness and credibility of creatine supplementation for muscle growth in older adults or those suffering from muscle-related disorders. Besides the application of creatine supplementation among older adults experiencing sarcopenia and those with muscle-related illnesses, this scoping review highlights areas for future therapeutic research and exploration, specifically focusing on the use of creatine alongside resistance training to address muscle wasting in patients facing cancer, end-stage renal disease, and heart failure.

FORENSIC IMPORTANCE

Creatine, although not a central element in several domains of forensic science, holds significant relevance, particularly in forensic toxicology and body fluid analysis, notably in urine. Here is a breakdown of its significance:

1. Integrity of Urine Samples:

Detection of Dilution or Substitution: Forensic urine analysis laboratories consistently measure creatinine levels to determine if a urine sample has been diluted with water or replaced with a non-urine liquid to disguise drug consumption.

Creatinine as a Marker: Creatinine is a metabolic byproduct of creatine phosphate found in muscles and is expelled in urine at a relatively stable rate. Unusually low creatinine levels (generally below 20 mg/dL, and critically under 5 mg/dL) indicate possible dilution or substitution.

Normalizing Drug Levels: In instances of diluted urine, some laboratories apply creatinine normalization to modify drug concentrations, yielding a more precise interpretation of drug screening results. This involves dividing the concentration of the drug by the creatinine concentration to adjust for dilution.

2. Identification of Urine:

Presumptive Analyses: The detection of creatinine serves as a crucial marker in presumptive tests for urine identification at crime scenes. The Jaffe test, an established technique, identifies creatinine through its reaction with picric acid, resulting in a red compound.

Urine-Specific Testing: Newer methods such as Uritrace® and RSID™-Urine also focus on creatinine or other urine components, such as Tamm-Horsfall protein, for presumptive identification.

3. Potential Insights into Health Conditions:

Kidney Health: While mainly utilized to evaluate urine dilution, creatinine levels can also indicate a person's kidney health. Elevated levels in blood or urine may signify underlying health issues, which could be pertinent in certain forensic scenarios (e. g. , investigations into the cause of death).

Muscle Mass: The excretion of creatinine correlates with muscle mass. Significant variations from anticipated levels may, in certain instances, offer indirect insights.

4. Detection of Creatine Use:

Increased Urinary Creatinine: Those using creatine supplements may show elevated urinary creatinine levels. This can be significant when interpreting drug testing results where dilution is presumed, as supplementation could marginally increase creatinine despite heightened fluid intake. Nonetheless, research indicates that supplementation is not an effective method for substantially raising creatinine levels to successfully mask dilution.

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