Effect of Creatine as a Supplement: A Mini-Review

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***Abstract*— Creatine is popular as a supplement, especially for strength and power activities. Even though most of the studies performed on creatine, have been focused on its efficacy as an ergogenic aid, there have been multiple therapeutic benefits as well. Creatine supplementation has been reported as beneficial for a plethora of medical conditions such as diabetes, heart disease, and sarcopenia. Additionally, creatine is an antioxidant, reducing the risk of progression of some cancers, reducing liver fat accumulation, minimizing bone loss, and increasing cognitive function in the aging population. Creatine is essential in cellular metabolism and the body's phosphagen energy system leading to better endurance and increased levels of energy in short time intervals such as during a sprint or a fast set of weightlifting. Usage of creatine, short-term or over a long period is safe, with no effects of renal dysfunction, gastrointestinal issues, musculoskeletal injuries, or cognitive functioning. This review article explains the benefits of creatine primarily from an athletic standpoint and concludes that creatine supplementation is safe with little to no side effects. Nevertheless, the quality and purity of creatine supplements vary significantly due to variable regulation and manufacturing procedures, which pose possible health concerns to consumers.**

Keywords—Creatine, ergogenic aid, metabolism, supplements, physical performance

I.INTRODUCTION

Creatine is a general ergogenic aid used by sportspersons of multiple sports backgrounds to increase physical strength and fat-free mass, decreasing protein breakdown, and enhancing physical performance by increasing anaerobic energy capacity [1 , 2]. Other than that, creatine has also been found to have therapeutic benefits regarding a variety of medical conditions like diabetes, sarcopenia, osteoarthritis, cancer, cognition, and cardiovascular fitness [3 , 4]. With over 40 years of research and 700 studies on human subjects backing its potential, creatine is coined as one of the safest sports supplements currently available [5]. Most of this research has been focused on creatine monohydrate although there is a wide variety of creatine forms such as creatine hydrochloride, creatine ethyl ester, and creatine phosphate commercially available [6]. Most of these research studies have been performed with a short-term supplementation of creatine which consisted of an intensive dosing phase followed by a reduced dosage maintenance phase with concurrent heavy resistance training [7]. Although a few studies have seen positive increases in long-term endurance training due to creatine supplementation, primarily it is seen that the impact of creatine diminishes as the duration of time performing an exercise increases [7]. Thus, this suggests that creatine is better utilized during short-term high-intensity exercises such as a fast set of heavy bench press repetitions or a sprint [7]. This review article aims to provide a comprehensive idea about the role played by creatine regarding different medical conditions and its efficacy as a sports supplement as well as the safety of creatine usage when administered over a long period.

II.CREATINE METABOLISM

Creatine (N-aminoiminomethyl-N-methylglycine) is a naturally occurring tripeptide constituted of the three amino acids glycine, methionine, and arginine and is synthesized in our bodies naturally at a rate of about 1g/day from arginine and glycine by arginine: glycine amidino transferase (AGAT) to guanidinoacetate (GAA). This GAA is then methylated by the enzyme guanidinoacetate N-methyltransferase (GAMT) with S-adenosyl methionine (SAMe) to form creatine. This biosynthesis of creatine is primarily done by the kidneys, pancreas, liver, and certain regions of the brain [4]. This endogenous synthesis of creatine accounts for around 50% of the daily requirement, and the other part should be found via one's diet which is unlikely to happen with a regular omnivorous diet since creatine is primarily found in raw, uncooked red meats but is exposed to high temperatures during the cooking process denatures it [8]. About 95% of the body's creatine is deposited in muscles with the other part saved in other tissues such as the heart, brain, and testes [9 , 10]. Over 60% of this creatine is in a phosphorylated form, complexed with inorganic phosphate (Pi) and deposited as phosphocreatine (P-Cr) with the other part saved as free creatine (Cr). The amount of creatine stored in one's body can be determined based on several reasons such as the prevailing muscle mass and skeletal muscle fiber type. On average, a 70kg person who upholds a regular diet including red meats and fish was found to have a total creatine pool of about 120 mmol/kg of dry muscle mass, which is around 120g-140g [11]. Due to their dietary restrictions, vegetarians are noted to possess muscle creatine and P-Cr levels Approximately 20-30% lower than that of non-vegetarians. Creatine uptake is controlled by multiple processes, including phosphorylation and glycosylation, as well as the extracellular and intracellular levels of creatine. This creatine is then transported to the cells by the transporters CreaT1 and CreaT2 which is predominantly present in testes [12]. Approximately 1-2% of the muscle mass creatine pool is degraded daily into creatinine which is then removed through urine [13 , 14]. The rate of degradation of creatine differs from individual to individual but is generally high when there is a greater muscle mass and elevated levels of physical exercise. Thus, to maintain optimum muscle creatine levels, a normal-sized adult might require consuming at least 2-3g of creatine per day. Wallimann and colleagues [15] reported that individuals with vegan or normal omnivore diets don't have saturated creatine stores. Since these diets typically provide either 0 or 0.75–1.5

g/day of creatine, daily dietary intake requirements may be around 2–4 g/day per person to support optimal general health.

Creatine plays a very important role in the body's energy supply. CreaT1 is mainly activated when the interior creatine levels of a cell go down and a mitochondrial isoform of CreaT1 transports creatine to the mitochondria. Creatine serves as a non-mitochondrial energy buffer, quickly transferring energy via a reversible process mediated by the creatine kinase enzyme. The energy yielded from the process of breaking down phosphocreatine into creatine and inorganic phosphate, which is around 10.3 kcals of free energy is used to resynthesize ATP via ADP + Pi [16 –20]. This shows the significance of creatine within the phosphagen energy system which largely contributes to rapid ATP generation in short time intervals of around 10s – 30s, which can greatly aid during intense physical exertion, where energy production is impaired or insufficient due to increased demand.

III. Benefits Creatine

While most of the studies on creatine are focused upon its benefits from a physical performance standpoint, creatine has also shown many therapeutic benefits. It has been reported that creatine supplementation, when done properly, saturates the muscle creatine stores, enhancing the acute exertion capacity [9 , 21] in athletes a variety of sports such as swimming [22 , 23], sprint performance [24], football [25] and in strength athletes [26] among others. Although most of these in research on males, creatine supplementation has been proven to have favorable benefits on females, children, adolescents as well as older populations. As a result of these studies, the International Society of Sports Nutrition has determined that creatine "is the most effective ergogenic nutritional supplement currently available to athletes in terms of increasing high-intensity exercise capacity and lean body mass during training" with the American Dietetic Association and American College of Sports Medicine reaching similar conclusions [26].

Apart from all the ergogenic benefits, creatine supplementation has also shown many benefits from a therapeutic standpoint. Creatine supplements have proven to decrease cholesterol and triglyceride levels better manage blood lipid levels reduce the lipid accumulation in the liver [27 – 30]. Creatine supplementation has additionally proven to decrease homocysteine, lessening the risk of heart disease [31]. It has also been found that creatine can reduce cancer risk [31] and act as an antioxidant. The additional benefits of creatine supplementation include increasing muscle mass and strength [11], reduction of bone loss, and increase cognitive function in aging populations [30 , 32].

A. Effects of Creatine on Physical Performance

When creatine is given as an oral supplement, the body's creatine pool increases. According to many studies, it can be seen indicating a positive relationship between muscle creatine uptake and exercise performance [21]. It was also seen that the body's fat-free mass significantly increased when creatine levels were increased. Concerning a meta-analysis conducted by Scott C. Forbes et al [30], supplementing with creatine alongside Intensive resistance training has demonstrated the potential to reduce body fat in adults over the age of 50 years. Volek et al [33] observed enhanced fat-free mass, physical performance, and muscle morphology in response to heavy resistance training after creatine supplementation of 25g per day for a week followed by a maintenance phase of 5g day-1 for 11 weeks. These results can be explained by the increase of the body's creatine pool, which leads to quicker adenosine triphosphate (ATP) regeneration between sets, enabling athletes to sustain a higher training intensity throughout their workouts. According to a 2003 meta-analysis [34], an average increase in muscle strength when performing 1RM (rep max), 3RM or 10RM resistance training was greater by 8% and a 14% greater weightlifting performance compared to the placebo group. R B Kreider and colleagues in their study on how creatine affected the performance in football players reported that creatine supplementation alongside a glucose /taurine /electrolyte supplement enhanced fat-free mass, bone-free mass, isotonic lifting volume, and sprint performance during high-intensity exercise [24].

Even though some researchers have shown positive effects, others have reported no statistically significant impact from creatine supplementation. Bemben et al have shown no additional positive effects by creatine supplemented combined with whey protein after 14 weeks of heavy strength training (3 days a week) to improve muscular strength and muscle mass in middle-aged men [11]. Another study reported that after 4 weeks of creatine supplementation in junior swimmers, it did not substantially enhance single sprint performance, but it did enhance swim bench test performance [22]. Jakobi et al also detected no impact of short-term creatine supplementation compared to the placebo group when performing isometric elbow flexion in both voluntary and stimulated contractions [35]. Although no effects were seen upon elbow flexion strength, significant weight gain was seen in the creatine group compared to the placebo group. These results may be caused by the possibility of the research subject groups majorly consisting of non-responders.

More recent scientific literature has conclusively found that creatine supplementation does show performance-enhancing and muscular development including a scientific summary consisting of over 100 citations reviewing the available knowledge up till 2007 published by the International Society of Sports Nutrition [9]. Hespel et al suggest that these anabolic effects have been a result of satellite cell proliferation, myogenic transcription factors and insulin-like growth factor-1 signaling [36]. This study also showed increased muscle glycogen storage and glucose transporter (GLUT4) expression, when creatine supplementation was done alongside training. Saremi et al [37] observed a difference in myogenic transcription factors when supplemented with creatine combined with heavy resistance training in healthy young males and found that the serum levels of myostatin which is a catabolic regulator of skeletal muscle mass decreasing in the creatine group.

Thus, according to most of the scientific literature, even though certain studies have identified no additional benefits of creatine supplementation, collectively it can be concluded that supplementing with creatine alongside heavy resistance training enhances physical performance in addition to promoting muscle hypertrophy.

B. *Effects of Creatine Supplementation on Skeletal Muscle Hypertrophy*

Other than increasing physical strength and enhancing ATP regeneration during exercise sets reducing fatigue, creatine supplementation has also shown an increasement of fat free mass by promoting muscle growth. Wu et al. found that Creatine is an effective supplement for boosting muscular strength, muscle mass, and athletic performance in healthy young people with proper training in a range of dosing schemes and sporting activities [38]. In a meta-analysis by Burke et al [39] shows that creatine supplementation, when combined with a structured resistance training program, fosters a modest increase in skeletal muscle hypertrophy in both upper and lower body muscles. This meta-analysis also suggests that these muscular hypertrophic benefits are greater in young adults compared to older individuals. Another study discovers greater improvements in 1RM, lean body mass, fiber cross-sectional area and contractile protein in trained young males when supplemented with creatine monohydrate combined with a multi-nutrient supplement and resistance training[40]. This research found improvements in body composition at the cellular and sub cellular-levels in resistance-trained participants which was a novel finding. It was conducted at a supplement loading dosage of 20g day-1 followed by a maintenance phase of 0.03g/kg/day[40]. The reduction of the serum levels of myostatin [37] also promotes muscle gain as myostatin isa muscle growth inhibitor and reduction of it allows skeletal muscle hypertrophy.

Deldicque et al performed a study where out of 9 subjects, a creatine group and a placebo (maltodextrin) group were chosen and the creatine group went through a loading phase of 5 days [41]. They commented on a 250% increment in collagen mRNA, a 45% increment in glucose transporter-4 (GLUT4) and a 70% increment in myosin heavy chain IIA levels. This study concluded that within the 5 days, creatine supplementation did not improve any anabolic signaling but increased the expression of certain targeted genes which are responsible in skeletal muscle hypertrophy [41].

According to many studies, creatine supplementation has also shown a rise in muscle insulin-like growth factor (IGF-1) concentrations. IGF-1 is a hormone that controls the growth hormone levels which directly impacts muscular growth. Burke et al [39] performed an 8-week research by supplementing 22 subjects (male and female) with creatine (0.25g/kg of lean body mass per day for 1 week followed by a 0.06g/kg of LMS for the next 7 weeks) and having a placebo group containing 20 subjects (male and female), with all the participants performing a regimented resistance training plan. A 67% increase in of intramuscular IGF-1 levels has been seen after the resistance training with a greater accumulation from the creatine group (78%) compared to the placebo group (54%). The study also found no difference in the IGF-1 levels between vegetarians and non-vegetarians as well as seeing similar results between the males and females. The authors hypothesized that the increase in muscle IGF-1 concentration in the creatine group may be attributed to the increased metabolic demand caused by a more rigorous training session. These enhancing effects could be caused by the increased total creatine stores in skeletal muscles. It is probable that the addition of creatine and the preceding rise in total creatine and phosphocreatine storage may have directly or indirectly improved muscle IGF-I production and muscle protein synthesis, resulting to an increase in muscle growth [39].

In summary, creatine supplementation has been demonstrated to enhance skeletal muscle hypertrophy when done concurrently with resistance training.

IV. Safety of Long-Term Creatine Supplementation

Given that creatine is one of the most popular performance-enhancing supplements currently available for athletes, numerous research has been carried out on the safety of creatine supplementation. Kreider et al. after conducting a study on supplementing with creatine monohydrate over a long period (up to 30g/day for 5 years) found that weight gain was a consistently reported side effect of creatine supplementation [24]. However, this weight was intramuscular water retention and fat-free mass. They concluded that none of the research shows that creatine supplementation leads to renal dysfunction, gastrointestinal issues, muscle cramping or musculoskeletal injuries. In actuality, they found that taking creatine as a supplement reduced the aforementioned anecdotally reported side effects. Longobardi I. et al [42] reported that creatine intake might enhance serum creatinine levels but has not shown any indications of renal dysfunction and has been proven to be safe for human use.

According to the Juhn MS et al [43] study, short-term use of creatine has not been demonstrated to cause any notable side effects. Juhn and Tarnopolsky [43] in their long term oral creatine supplementation study concluded that neither short-term nor long-term supplementation resulted in any harmful effects on the kidneys of healthy persons. Similar conclusions were drawn by Baracho et al. [44] where they stated that oral creatine supplementation did not lead to kidney or liver toxicity.

Based on the above research, it can be concluded that creatine usage, short-term or over a long period of time is safe or does not cause any detrimental side effects.

V. Challenges of Creatine as a Supplement

Creatine supplementation is highly popular among athletes due to its possible performance-enhancing effects; nonetheless, it poses substantial quality and purity concerns that must be carefully addressed [45 , 46]. The lack of consistency among creatine supplements on the market might be related to many important variables. For example, the lack of FDA regulation leads in a huge discrepancy across products, making it difficult for customers to comprehend the composition of the supplements they are purchasing [47]. Also the manufacturing process of creatine supplements might introduce potentially hazardous chemicals such as dicyandiamide, dihydro triazines, and creatinine, which must be carefully monitored to assure user safety [46]. Research suggests that some products may contain harmful amounts of heavy metals, which can accumulate in the body and create health difficulties [48]. The creatine supplement industry provides several products, including creatine monohydrate, creatine ethyl ester, buffered creatine, and micronized creatine. While creatine monohydrate is the most researched and extensively utilized, other types are marketed for their alleged benefits, although the data supporting these claims is sometimes lacking [49]. The lack of defined techniques for

testing the safety of creatine in humans raises concerns regarding contaminants and appropriate doses, as the quality control standards of these products may not meet those of medicines [45].

Also commercially marketed creatine supplements do not have the same stringent quality control requirements as medicines since they follow lower Dietary Supplement Health and Education Act (DSHEA) regulations. As a result, it is difficult to adapt the effectiveness and safety findings from published studies to everyday practice. A commercially accessible product's dosage may be higher or lower than the labeling suggests. This might affect creatine's efficacy. Lack of appropriate quality control might result in contaminants in creatine supplements, that might result in unexpected negative consequences [45]. This gap in quality control might result in changes in creatine content in supplements, possibly exposing consumers to contaminants or wrong doses, emphasizing the need to ensure the purity and quality of creatine supplements for consumer health and safety.

VI. Conclusion

When considering creatine, especially creatine monohydrate, it remains one of the few ergogenic aids that have dependably proven to be effective and safe for human consumption. Given that many studies have observed strength gain, muscle hypertrophy, fat-free mass gain and performance enhancement in physical exercises, the efficacy of creatine as a performance-boosting supplement for athletes is undenied. Additionally, creatine supplementation has also shown a number of other therapeutic effects in regard to other medical conditions as well. With many studies proving that creatine does not have any detrimental side effects, it can be concluded that it is an effective and safe ergogenic aid. However, ensuring the purity and quality of creatine supplements is critical for user safety considering possible impurities and dose variations.

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