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An Update on Effects of Creatine Supplementation on Performance: A Review

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Abstract

Supplementary creatine, available in many different forms but most commonly monohydrate, is a legal and reportedly safe to consume nutritional ergogenic aid. After searching internationally recognised research databases, this review provides and update on the current literature on the physiological effects of creatine supplementation on performance whilst also discussing the underlying physiology regarding the synthesis and dietary provision of creatine as well as addressing issues of safety and the ethical considerations of usage. Research has shown that regular consumption of supplementary creatine can raise associated content within skeletal muscle. Subsequently, there is an extensive, and still growing, body of the literature supporting the efficacy of creatine supplementation on enhancing exercise performance, exercise tolerance, muscle strength and lean body mass. Moreover, little scientific evidence exists showing any unfavourable effects on individuals who are free from illness and disease. This review consolidates the current literature and provides application to the athletic setting which is purposeful for those choosing to either recommend or consume this nutritional ergogenic aid. At this current time, a traditional loading and maintenance supplementation protocol is advised as contemporary research studies are still to unravel the benefits of alternative approaches.

Keywords: Creatine monohydrate; Exercise performance; Narrative review

Abbreviations

ATP: Adenosine Triphosphate; ADP: Adenosine Diphosphate; CR: Creatine; CK: Creatine-kinase; CRM: Creatine Monohydrate; PCr: Phosphocreatine

Introduction

Creatine (CR), a substance produced naturally within the human body, was initially discovered by the French scientist Chevreul in 1835, and named after the Greek word 'kreas', meaning flesh [1]. By the early twentieth century CR could be pharmaceutically produced and the first nutritional CR supplementation studies were trialed [2,3]. However, it wasn't until the early 1990's that CR came into the public view following the 1992 Barcelona Olympics. Following these games several British Olympic athletes admitted to using CR after winning gold medals in their events [4]. By 1993, the first commercially available CR supplements were on the general market, classified as nutritional ergogenic aids [5]. CR is considered to be one of the most comprehensively studied and 'relatively' safe [6] ergogenic aids available to athletes.

Many varieties of CR have been formulated with the intention of increasing the proposed benefits (such as creatine citrate, creatine ethyl-ester, creatine gluconate). To date, creatine monohydrate (CRM) is the most widely used and scientifically researched form available, with over 2.5 million kilograms produced each year for oral supplementation alone [7,8]. There have been numerous studies focusing on highlighting the beneficial effects of supplementing with CR, with many recording significant performance effects. Reported performance enhancing properties of this supplement include, increased maximal work output [9], increased maximal strength [10], increased fat-free mass [11], decreased blood lactate accumulation [12] as well as promoting faster regeneration of adenosine triphosphate (ATP) during high intensity interval exercise [13]. Numerous studies illustrate that CR supplementation actively increases neuromuscular performance during short duration, anaerobic, intermittent exercises and is very beneficial to high power requiring athletes [13-16]. Interestingly, CR supplementation has shown to negatively affect range of motion [17] and does not influence field-based studies testing aerobic capacity [18].

Creatine synthesis

The guanidine compound of CR, or α-methyl-guanidinoacetic acid, is a naturally occurring, nitrogenous amino acid composition, synthesised from three amino acids: glycine, arginine and methionine, and three enzymes: L-arginine:glycine amidinotransferase (AGAT), methionine adenosyltransferase (MAT) and guanidinoacetate methyltransferase (GAMT) [1,13,19,20]. The endogenous production of CR is initiated in the kidney by the transfer of arginine to glycine, (catalysed by AGAT), yielding L-ornithine and guanidinoacetate. This guanidinoacetate is then transported to the liver (hepatocyte cells) by the blood and methylated by S-adenosyl-L-methionine. This reaction produces free-form CR and S-adenosyl-L-homocysteine [1,19,21]. Storage occurs predominantly in the skeletal muscle (approximately 95%) with the remaining 5% distributed between the heart, brain, liver, kidneys and testes [22]. The muscle fibres are unable to synthesize CR and it must be absorbed and transferred via the blood, through the use of a specific protein; CR transporter protein, which enables distribution of CR throughout cells.

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Dietary Creatine

A demand for CR is met by both, intestinal absorption from the diet (1-2 g/d), and endogenous production (1-2 g/d), with research showing that the latter is regulated by the former, and thus reduces if CR consumption is increased through supplementation or other dietary interventions [21]. The average CR pool (male: 70 kg) is approximately 120-140 g, although this varies depending on fat-free mass [23] and skeletal muscle fibre type [22]. In general, oral supplementation aims to enhance this CR pool, with research showing a maximum increase of approximately 20% following a high dosage loading programme [13]. Although it is possible to consume CR rich foods (Table 1) and increase dietary intake naturally, it would potentially be counterproductive to athletic performance due to a subsequent rise in protein and lipid consumption. Furthermore, it has become apparent that with nearly all sources of CR coming from animal products, it is very difficult for the vegetarian/vegan athlete to increase intake outside of supplementation [24,25].

Research has shown that excess supplementation with CR (>30 g/d) will generally result in cell saturation, after which surplus CR will be removed from the body by renal filtration. While some claim this can lead to an increased load on both the liver and kidneys, empirical research is yet to find any such side effects in healthy individuals [26,27]. It is also worth noting that once supplementation has ceased, serum CR levels will return to their pre-supplementation level within a 30-day period [22].

Food source	Serving	Creatine content (g)
Herring	225 g/8oz	2.0 - 4.0
Pork	225 g/8oz	1.5 - 2.5
Salmon	225 g/8oz	1.5 - 2.5
Beef (lean)	225 g/8oz	1.5 - 2.5
Milk (1% Fat)	250 ml/8oz	0.05

Table 1: Creatine content as present in raw food products [28].

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Methodology

Materials and Methods

A range of databases, including PubMed, Google Scholar and EBSCO-host, were searched using terms concerning CR supplementation and athletic performance; including 'creatine', 'supplementation', 'high intensity training', 'ergogenic aid', 'performance', 'health', 'side effects', 'resistance', 'athlete', 'muscle strength', muscle power' and 'adaptations'. Studies evaluating the effects of CR supplementation on exercise performance in humans were selected for inclusion. Further references were found, appraised and included from the bibliographies of selected research articles.

Result

General Ergogenic properties

Once in the muscle, at rest, CR is phosphorylated by creatine-kinase (CK) to form phosphocreatine (PCr), an important substrate in the generation of muscle force production [29,30]. In the rest-to-exercise transition, the muscles begin to consume stores of adenosine triphosphate (ATP) by breaking the phosphoanhydride bonds. At this stage, the high energy yielding phosphoryl group of PCr is transferred to adenosine diphosphate (ADP) to resynthesize ATP (re-phosphorylation), facilitating a greater intensity of work to be sustained [9]. This system acts as a temporal energy buffer, providing the majority of energy for the first 6-8s of muscular work. As PCr stores deplete, and ATP resynthesis diminishes, anaerobic glycolysis becomes the predominant energy source [28]. It has been theorized that the volume of PCr existent within the muscles will significantly influence the amount of energy generated during short periods of high intensity exercise [31,32], with early research by Katz et al. [33], stating that fatigue is more closely related to low PCr stores than high lactate content.

Creatine and strength training

A classic CR research study reported an increase in strength performance following 12 weeks of supplementation when combined with heavy resistance training (80% one repetition maximum) [34]. In this study, participants ingested 25 g/day CR for seven days (loading phase), followed by 5 g/day CR for the remainder of the study (maintenance phase). The participants significantly increased their muscular strength, fat free mass (FFM), muscular hypertrophy and total muscle CR concentrations over a control group. It was suggested that the significant effects recorded were accredited to an increased total CR pool, enabling a greater regeneration of ATP between exercise sets. Contemporary research has continued to explore CR administration and concurrent strength training, with numerous studies reporting similar significant ergogenic effects following supplementation protocols [10,11,35,36].

Contradictory research by Bemben et al. [37] showed no additional benefits of supplementing CR when combined with a 14-week resistance training programme [37]. Participants ingested a placebo, 5 g of CR or 5 g of CR together with 35 g whey protein. While all trials showed improved muscular strength, there were no significant differences witnessed between groups. These conflicting results can partly be explained due to the lack of a pre-loading supplement protocol as recommended within CR research [38,39], and also due to supplementation occurring on training days only (three a week) as opposed to research based recommendations of throughout entire training protocol [40,41].

Creatine and intermittent/recurrent high intensity exercise

Numerous researchers have focused on the effects CR supplementation has on intermittent, high intensity exercise, with many reporting improved performance varied supplementation protocols [42-45]. Early research conducted by Yquel et al. [46] evaluated the effects CR ingestion had on muscle power output and PCr resynthesis during recurrent bouts of maximal exercise. Participants performed eight bouts of maximal plantar flexion both pre and post CR ingestion interspaced with 30s recovery. Both muscle power output and PCr resynthesis increased following completion of supplement protocol. Conclusions were drawn that the better conservation of muscle power output observed, following CR ingestion, was attributed to a greater resynthesis of PCr throughout the exercise protocol.

A further study examined the effects CR supplementation on blood lactate and time to exhaustion during incremental cycling exercise [12]. Subjects completed a maximal incremental test to exhaustion both before and after six days of CR supplementation. Lactate concentrations were significantly reduced during exercise following supplementation, with both time to exhaustion and maximal power output listed as approaching significant. It was concluded that the findings established that CR supplementation significantly reduces lactate concentrations during high intensity, intermittent exercise.

Creatine and endurance exercise

Although predominantly associated with short duration high intensity exercise, there is some evidence to support CR supplementation alongside long term aerobic activities. Early research conducted by Chwalbinska-Moneta [47] examined the effects 20 g/d of CR had on the endurance performance of elite male rowers. Subjects were randomly assigned to either a placebo or supplement group, before completing an incremental exercise test on a rowing ergometer. Blood lactate and heart rate were taken throughout and time to exhaustion was logged. Both the mean individual lactate threshold and time to exhaustion rose significantly in the CR group when compared to the placebo group. The study concluded that the results gained indicted that CR supplementation increases lactate threshold and thus improves endurance in rowing.

Opposing research is more prominent in this area, with early research Thompson et al. [48] reporting six weeks of CR supplementation had no effect on aerobic endurance of female swimmers. A further meta-analysis conducted by Branch [18] highlighted that any endurance activities lasting longer than 150s rely on oxidative phosphorylation as a primary energy supply, and so once this mark is exceeded, the ergogenic potential of CR diminishes.

Creatine and exercise: Summary of creatine and exercise performance

Supplementation with CR has been shown to be an effective ergogenic aid across a range of sporting intensities. It is well established that CR supplementation has an ergogenic effect on both strength training and single and recurrent bouts of short duration high intensity exercise, with contemporary studies showing a positive effect from as little as seven days supplementation [44,49]. There are numerous mechanisms by which CR supplementation acts to augment athletic performance. During the CK reaction, CR is substrated resulting in the generation of PCr. As previously mentioned, PCr is responsible for the re-phosphorylation of ADP to ATP during bursts of high intensity movements, and therefore greater quantities result in increased energy availability [50]. As PCr stores decline, phosphofructokinase production is stimulated, increasing the rate of glycolysis [51]. At this stage, CR has been shown to buffer the pH changes that occur during the accumulation of lactate and hydrogen ions, delaying the onset of acidosis and subsequent fatigue.

With regards to longer bouts of physical exertion, a lack of contemporary research exists. However, the majority of available research has shown CR to have little to no ergogenic benefits as exercise exceeds 150s [18]. This is due to a change in how energy is supplied (oxidative phosphorylation as opposed to PCr-CR system) to the requiring muscles.

Safety and ethical considerations

Since the late 1900's CR has continuously gained popularity as a supplement among the athletic population [52]. The use of this dietary intervention has been surrounded by both misconception and debate; with the media claiming that CR supplementation is both dangerous and unethical [31]. Many anecdotal claims concerning CR still in the include muscle cramping, dehydration, liver damage and gastrointestinal distress. While it is conceivable that athletes may experience these symptoms, contemporary research has shown that athletes are at no greater risk, and in fact, potentially a lesser risk of these symptoms, than those not supplementing with CR [53-55].

One of the more recurring claims associated with CR is that of increased renal distress through prolonged supplementation. Early research completed by Pritchard and Kalra [55] reported that CR supplementation had a deleterious effect on the renal function of a single participant following a 7 week supplementation programme. They recorded moderate decreases in renal function were recorded over time, and thus it was concluded this was strongly linked to the CR supplements that were being administered. However, future research highlighted concerns over the practices adopted during this study, stating that there was no scientific backing to the claims made due to the single participant already suffering from recurring renal failure [56]. A further report from Mesa et al. [1] concluded that due to the distorted information gathered and reported, the case report was very misleading. Table 2 summaries the current literature which has revealed that CR supplementation at several different dosages has had no adverse findings on renal kidney functioning.

Authors	Sample	Sample characteristics	Supplementation protocol	Renal problems recorded
Terjung et al. [4]	7	Healthy females	20 g/d for 5 days + 3 g/d for 8 weeks	No
	7	Healthy males	20 g/d/ for 5 days	No
Gualano et al. [27]	18	Trained males	10 g/d for 12 weeks	No
Gualano et al. [26]	1	Healthy male with one kidney	20 g/d for 5 days + 5 g/d for 30 days	No
Gualano et al. [27]	25	Males and females with type 2 diabetes	5 g/d for 12 weeks	No
Neves JrM et al. [27]	13	Postmenopausal women	20 g/d for 1 week + 5 g/d for 11 weeks	No
Terjung et al. [4]	48	Healthy males and females	3 g/d for 1 week + 20 g/d for 8 weeks	No
Liddle et al [30]	26	Resistance trained males	20 g/d for 1 week + 5 g/d for 11 weeks	No

Table 2: Research studies examining effects of creatine supplementation on renal function in adults.

It would be difficult to consume the recommended dosages of CR via a balanced nutritious diet, and therefore supplementation is an obvious choice by athletes. In order for an athlete to gain enough CR to effectively equate to a loading strategy, it would require 3-4 kg of certain foods to be consumed for a period of 1-2 days. Despite being potentially unpalatable for most, a significant increase is lipids and proteins would but an unwanted addition. Furthermore, those with specific dietary requirements may struggle to consume CR rich foods due to restrictions i.e., vegetarians, vegans, religious diets. CR is not banned by any organization however the USA National Collegiate Athletic Association has a policy which restricts creatine provision to athletes from member teams [8]. With research showing that CR is safe to consume, even for prolonged periods (Table 2), it has been suggested that those advocating for restrictions are merely aware of the anecdotal misconceptions surrounding the supplement, and not the empirical based evidence. It has been Buford et al. [31] proposed that there is no difference between following a CR supplementation programme to increase PCr stores, and completing a carbohydrate loading programme to enhance glycogen stores [31]. It is worth noting that many researchers have argued that banning CR would in fact be unethical as it has been linked to reductions in musculoskeletal injuries [57], heat stress [58], and decreases in rehabilitation periods [59], as well as being a naturally occurring compound.

Recommendations

CR supplementation has been shown to positively impact upon performance across a range of sports, with the most prominent literature focusing on short-term, intermittent/recurrent, high intensity activities [45]. Specifically, there is strong evidence to suggest CR increased power output [43], repeated sprint ability [60], maximal strength [50] and FFM [11].

A typical CR supplement protocol reported comprises of by Mesa et al. [1] has a loading phase lasting 1-2 days (4 × 5 g CR over 5-7 hr intervals), followed by a maintenance phase for continuous supplementation thereafter (3-5 g CR per day). The majority of research surrounding CR and its ergogenic potential has used very similar protocols, with many reporting significant improvements across a range of variables. However, more recent research by Cooper et al. [13] found that a moderate protocol consisting of 1 g doses taken over ten hours (1 g every 30 min, 20 g CR in total) for five days, resulted in reduced urinary CR when compared to a typical supplementation protocol. It was estimated that this decrease in urinary CR equated to an increase in TCr by 13%, further increasing PCr stores and thus energy potential.

Conclusion

The use of CR as a dietary supplement is prevalent across amateur and professional athletes alike. With research showing a performance increase of 1% can be the difference between Olympic gold and not making the final, it is understood why athletes will turn to ergogenic aids to potentially gain an advantage [61]. Supplementation with CR has been advocated to improve both short-term and intermittent high intensity exercise, with some supporting literature for both mid and long-term bouts. Currently, no scientific evidence exists showing any unfavorable effects, even when supplementation is prolonged, providing correct protocols are followed and the participant is otherwise healthy.

It is recommended that those considering supplementation first establish a sound dietary foundation, ensuring a balance in the foods consumed as well as maintaining constant hydration [62]. Furthermore, supplementation will be insignificant in producing desired results without an appropriate training stimulus (e.g. a specific resistance based training programme). With regards to the supplementation protocol adopted, at this stage it is recommended that an athlete follow a traditional loading/maintenance programme as opposed to that recommended by contemporary research by Cooper et al. [13], as further examination research is needed to fully establish the benefits of novel and alternative protocols and whether alteration of the initial loading phase results in significantly greater outcomes.

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