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





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Part II. Common questions and misconceptions about creatine supplementation: what does the scientific evidence really show?

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ABSTRACT

Creatine monohydrate supplementation (CrM) is a safe and effective intervention for improving certain aspects of sport, exercise performance, and health across the lifespan. Despite its evidence-based pedigree, several questions and misconceptions about CrM remain. To initially address some of these concerns, our group published a narrative review in 2021 discussing the scientific evidence as to whether CrM leads to water retention and fat accumulation, is a steroid, causes hair loss, dehydration or muscle cramping, adversely affects renal and liver function, and if CrM is safe and/or effective for children, adolescents, biological females, and older adults. As a follow-up, the purpose of this paper is to evaluate additional questions

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and misconceptions about CrM. These include but are not limited to: 1. Can CrM provide muscle benefits without exercise? 2. Does the timing of CrM really matter? 3. Does the addition of other compounds with CrM enhance its effectiveness? 4. Does CrM and caffeine oppose each other? 5. Does CrM increase the rates of muscle protein synthesis or breakdown? 6. Is CrM an anti-inflammatory intervention? 7. Can CrM increase recovery following injury, surgery, and/or immobilization? 8. Does CrM cause cancer? 9. Will CrM increase urine production? 10. Does CrM influence blood pressure? 11. Is CrM safe to consume during pregnancy? 12. Does CrM enhance performance in adolescents? 13. Does CrM adversely affect male fertility? 14. Does the brain require a higher dose of CrM than skeletal muscle? 15. Can CrM attenuate symptoms of sleep deprivation? 16. Will CrM reduce the severity of and/or improve recovery from traumatic brain injury? Similar to our 2021 paper, an international team of creatine research experts was formed to perform a narrative review of the literature regarding CrM to formulate evidence-based responses to the aforementioned misconceptions involving CrM.

1. Introduction

Creatine (methylguanidine-acetic acid) was first isolated in the 1830's [1] but it was not until the 1990's when creatine monohydrate research really emerged following seminal studies by Harris et al. [2] and Hultman et al. [3] who found that different dosages of CrM influenced plasma and intramuscular creatine levels. To date, there are ≥ 1000 peer-refereed papers involving CrM [4]. Collectively, CrM appears safe [5–7] and is one of the most effective dietary interventions for improving aspects of sport, exercise performance and health across the lifespan [4,8,9]. Despite the wealth of knowledge regarding CrM and robust body of literature supporting the diverse benefits, numerous questions and misconceptions about CrM remain prevalent. To initially address some of these questions and misconceptions, we published a narrative review 'Common questions and misconceptions about creatine supplementation: what does the scientific evidence really show' [10]. This paper addressed whether CrM leads to water retention and fat accumulation, is a steroid, causes hair loss, dehydration or muscle cramping, adversely affects renal and liver function, and if CrM is safe and/or effective for children, adolescents, biological females and older adults.

Despite the initial paper, many questions and misconceptions regarding CrM remain prevalent in social media and clinical practice. These include but are not limited to: 1. Can CrM provide muscle benefits without exercise? 2. Does the timing of CrM ingestion really matter? 3. Does the addition of other compounds with CrM enhance its effectiveness? 4. Does CrM and caffeine oppose each other? 5. Does CrM increase the rates of muscle protein synthesis? 6. Is CrM an anti-inflammatory intervention? 7. Can CrM increase recovery following injury, surgery and/or immobilization? 8. Does CrM cause cancer? 9. Will CrM increase urination? 10. Does CrM influence blood pressure? 11. Is CrM safe to consume during pregnancy? 12. Does CrM enhance performance in children and adolescents? 13. Does CrM adversely affect male fertility? 14. Does the brain require a higher

dose of CrM than skeletal muscle? 15. Can CrM attenuate symptoms of sleep deprivation? 16. Will CrM reduce the severity of and/or improve recovery from traumatic brain injury?

To address these questions, an internationally renowned team of creatine research experts was again formed to perform a narrative review of the literature regarding CrM to formulate evidence-based responses to misconceptions mentioned earlier involving CrM.

2. Can CrM provide muscle benefits without exercise?

Creatine is primarily stored within skeletal muscle and helps facilitate the production of adenosine triphosphate (ATP) within the cell, thereby serving an important role in energy production. As a result, there is some evidence that CrM (without an exercise intervention) can significantly increase total creatine stores and may improve exercise performance [11]. For example, Harris et al. [2] and Hultman et al. [3] showed that a 4.5–10 day CrM protocol at ~20 grams/day (referred to as creatine-loading) could increase the total creatine pool (phosphocreatine [PCr] and free creatine; mmol/kg dm) in human muscle. Similar increases in the skeletal muscle creatine pool were seen with the ingestion of 3 grams/day for 28 days [3]. Increased intramuscular creatine levels may help explain some of the improvements observed in the literature on upper- and lower-body strength, anaerobic and physical working capacity, and sprint performance in a hot and humid environment [12–17] in healthy, despite no exercise intervention.

Syrotuik and Bell [18] found that individuals who exhibited a significant increase in total intramuscular creatine (greater than 20 mmol·kg⁻¹ dry weight) after a 5 day CrM loading protocol, termed “responders,” demonstrated significant improvements in strength. However, not all participants exceeded this 20 mmol·kg⁻¹ dry weight threshold. The individual responsiveness to CrM varies depending on several factors, including low resting (pre-supplementation) muscle creatine stores, age, biological sex, type II muscle fiber percentage, physical activity patterns, and habitual dietary intake of creatine [18–20]. Individuals who adhere to vegan, vegetarian, or emphasize plant-based diets tend to have lower baseline creatine levels compared to those on omnivore or carnivore diets due to the absence or reduction in creatine-rich animal-based foods (i.e. seafood, meat) and may respond differently to CrM strategies [21,22]. For example, Watt et al. [23] found that CrM (0.4 grams/kg/day for 5 days or ~30 grams/day) significantly increased muscle total creatine content more in vegetarians ($n=7$; 28 years of age) compared to non-vegetarians ($n=7$; 23 years of age; consumed ≥ 2 servings of meat/week). Whether this translates to greater improvements in muscle performance without exercise remains to be elucidated. Furthermore, older adults (>65 years) may respond favorably to CrM as there is some evidence that they have reduced skeletal muscle creatine stores compared to younger adults [19] and experience a decline in lean tissue mass, strength, and power over time [24]. Subsequently, CrM may be a viable and effective strategy to offset these age-related consequences of biological aging [19]. Further, CrM alone has resulted in delayed measures of fatigue in older adults. The Physical Working Capacity at Fatigue Threshold (PWCFT), a submaximal cycle ergometer test developed by deVries et al. [25], is useful for evaluating the capacity for physical work, the ability to delay fatigue, and for screening older individuals at risk for sarcopenia [26]. Stout et al. [27] reported that 14 days of CrM (20 grams/day for 7 days followed by 10 grams/day for 7 days) without an exercise intervention significantly increased PWCFT by 15.6% and grip strength by 6.7% in

men and women aged 64–86 years. Although this increase in PWCFT was approximately half of the 28% increase observed in the study by deVries et al. [28], which examined 10 weeks of moderate-intensity endurance training, the improvement in PWCFT with CrM alone is still notable, considering the absence of exercise. Forbes et al. [11] performed a narrative review summarizing the small body of research examining the efficacy of CrM without exercise training and concluded that CrM improved measures of fat-free mass, functional ability (i.e. sit-to-stand), and reduced lower-body fatigue. It is important to note that the majority of studies included in this review used a CrM “loading” phase (20 grams/day for 7–10 days) or high daily dosages (17–26 grams/day) of CrM. Studies that did not utilize a CrM loading strategy failed to observe any beneficial effects [29,30].

In summary, CrM can provide some muscle performance benefits even without exercise. Populations with lower baseline creatine levels, such as vegans and vegetarians, may experience a greater response to CrM.

3. Does the timing of CrM ingestion really matter?

The notion that the timing of CrM (in close proximity to exercise) may influence the physiological adaptations from exercise (primarily resistance training) has historically relied on speculative mechanisms (for reviews, see Candow et al. [31] and Ribeiro et al. [32]). Exercise-induced hyperemia, which is influenced by exercise duration and intensity [33,34], could theoretically affect the delivery and uptake of creatine by skeletal muscle [35,36], though this effect is suppressed shortly (~30 minutes) after exercise cessation. In this context, a single dose of CrM (i.e. 5 grams) may take up to 2 hours to achieve peak levels in the blood following ingestion [2], rendering CrM supplementation immediately before, during, or after a typical resistance training session (e.g. 40–90 minutes) [37] most likely insignificant [32,38]. However, exercise may also modulate sodium (Na^+)/potassium (K^+) pump activity, which could contribute to creatine transport and accumulation in active tissues [39,40]. Therefore, similar to hyperemia, pre-exercise CrM-induced elevation in circulating creatine levels could work in conjunction with Na^+/K^+ pump activation, thus theoretically favoring tissue uptake and retention. The effect of skeletal muscle contractions on enhanced creatine uptake has been shown over the short term [2]; however, it is unknown whether this may favor longer-term creatine storage past its saturation in skeletal muscle. In theory, CrM timing may be more relevant during the initial stages of a supplementation regimen to enhance creatine uptake and retention until saturation is achieved [38].

Studies directly investigating the timing of CrM are scarce and most lack adequate experimental control (i.e. placebo comparator) and have small sample sizes resulting in low statistical power. Despite Cribb and Hayes [41] showing greater total muscle creatine (and glycogen) levels in bodybuilders supplementing immediately before and immediately after each resistance training session vs. supplementing in the morning and evening; this was a single-blinded experiment using a multi-ingredient supplement containing protein and carbohydrates, limiting further conclusions. More recently, Forbes et al. [42] showed similar effects in muscle strength and regional muscle thickness gains after either pre- or post-resistance training CrM (0.1 grams/kg/day for 8 weeks) in young recreationally active adults ($n = 10$). These results have been further corroborated by Candow et al. [43], Antonio and Ciccone et al. [44], Jurado-Castro et al. [45] and Dinan et al. [46], all

showing similar effects in resistance training-induced adaptations, independent of the timing of CrM. In the only study that compared the strategic timing of CrM to a placebo group, Candow et al. [47] reported similar changes in whole-body lean tissue mass (as measured using dual-energy x-ray absorptiometry) and muscle strength (leg press and chest press 1-repetition maximum) after 32 weeks of CrM (0.1 grams/kg or ~8 grams immediately before or after each resistance training session; 3 x/week) in healthy older adults (≥ 50 years of age). Interestingly, the group who consumed CrM post-exercise had greater improvements in whole-body lean tissue mass over time compared to the placebo group. Additionally, there were no differences in whole-body lean tissue mass increases between the pre-exercise CrM group and placebo group. Certainly, the existing literature on the topic has notable limitations, such as a lack of actual creatine retention measurements, precluding the ability to directly determine the time course of creatine uptake during a resistance training program as a function of its supplementation strategy, thus warranting further research.

In summary, the current body of evidence does not validate that the timing of CrM is critically important in relation to long-term resistance training, as both pre- and post-exercise CrM seem equally effective in promoting resistance training-mediated gains in lean tissue accretion and muscle performance. Consistent ingestion of CrM during a resistance training program is likely the most important variable to consider.

4. Does the addition of other compounds to CrM enhance its effectiveness?

CrM is effective whether it is co-ingested with other nutrients or not [8,48]. However, there is evidence that creatine uptake into skeletal muscle can be enhanced by glucose ingestion and/or insulin [49–53]. For example, Green et al. [54] reported that the combination of CrM (5 grams), dextrose (18 grams) and glucose (95 grams) promoted greater muscle creatine retention over time. Additionally, Nelson et al. [55] and Roberts et al. [36] showed that CrM had favorable effects on glycogen resynthesis. Burke et al. [56] examined the combined effects of CrM with alpha-lipoic acid (known to enhance glucose uptake) and sucrose compared to CrM and sucrose or CrM alone on intramuscular creatine uptake and retention. Results revealed a significantly greater increase in intramuscular phosphocreatine and total creatine in the CrM, alpha-lipoic acid and sucrose group compared to the other groups. Despite greater increases in creatine uptake and retention over the short term, there is limited evidence that the combination of CrM and carbohydrates or other insulin-sensitizing nutrients lead to greater changes in body composition or performance (i.e. increases in muscular strength), or that it affects the maximal levels attained after a period of supplementation.

In addition to carbohydrates, there has been some interest as to whether protein or a metabolite of the essential amino acid leucine (i.e. beta-hydroxy-beta-methylbutyrate [HMB]) can enhance the effectiveness of CrM. For example, Steenge et al. [49] reported that CrM (4 x 5 grams/day) with either a high amount of carbohydrates (96 grams) or moderate amount of carbohydrates (47 grams) plus 50 grams of protein resulted in greater creatine uptake and retention compared to CrM. Cribb et al. [57] and Cornish et al. [58] reported that CrM combined with carbohydrate, whey protein and/or conjugated linoleic acid (CLA) promoted greater gains in strength and lean tissue mass. There is also some evidence that CrM (0.1 grams/kg/day) and whey protein (0.3

grams/kg/day) increased lean tissue mass (+5.6%) and bench press strength (+25%) after 10 weeks of resistance training in healthy older males compared to CrM or placebo [59]. However, others have not observed the same benefits from CrM and protein [60,61]. In regards to HMB, the change in absolute power achieved at 8 mmol/L of lactate was greater in the CrM plus HMB group compared to either CrM or HMB alone or placebo during a rowing exercise test in endurance-trained young male [62]. In contrast, others have not found greater benefits from the combination of CrM and HMB supplementation on changes in body composition or muscle performance compared to CrM alone [59–61,63].

In regards to other possible potentiating ingredients, CrM with sodium bicarbonate (e.g. 0.3 grams/kg/day) promoted greater performance benefits (e.g. repeated sprint performance, soccer specific performance, and anaerobic performance) than CrM or sodium bicarbonate alone [64–67]. Similarly, CrM with β -alanine provided additive benefits in vertical jump [68], and resulted in greater gains in lean tissue mass in power lifting athletes compared to creatine alone [69]. However, the combination of CrM and β -alanine failed to improve physical working capacity at the neuromuscular fatigue threshold [70], or VO_2 peak, time to exhaustion, power output or oxygen uptake associated with ventilatory threshold or lactate threshold [71]. Kerksick et al., [72] examined the effects of CrM (20 grams/day for 5 days; 5 grams/day for remaining 23 days) with and without D-pinitol during 4 weeks of resistance training in young resistance-trained males. Intramuscular creatine stores and upper-and lower body muscular strength increased similarly in both groups; however, the CrM group experienced greater improvements in lean tissue and fat-free mass ($p < 0.05$) compared to the CrM and D-pinitol group [72]. Further, Taylor et al. [73] had resistance-trained men ($n = 47$) ingest either 5 grams of CrM + 70 grams of dextrose, 3.5 grams of CrM with 900 mg fenugreek extract or a placebo (70 grams of dextrose) for four days a week for 8 weeks. Participants ingesting CrM experienced similar changes in lean tissue mass and muscle strength compared those on placebo. Similarly, co-ingesting CrM with cinnamon extract (0.5 grams) [74] and Russian tarragon (0.5 grams 30 minutes before ingesting creatine) [75] does not affect whole-body creatine retention, muscle-free creatine, or anaerobic sprint capacity. Additionally, since creatine uptake into the cell increases intracellular hydration, research has evaluated whether co-ingesting CrM with glycerol and water can promote greater fluid retention than glycerol with water [76–78]. These studies generally indicate that co-ingesting creatine (e.g. 11.4 grams/day) with glycerol (2×1 grams/kg/day) for 7 days increases total body water [77,79] without altering plasma volume [76] thereby improving thermoregulation during exercise in hot and humid environments [76,77,79].

In summary, there is some evidence that the combination of CrM with other purported ergogenic compounds (i.e. carbohydrate, protein) can accelerate intramuscular creatine accumulation and potentially increase exercise-related training adaptations.

5. Does CrM and caffeine oppose each other?

Combined ingestion of CrM and caffeine is common due to the daily ingestion of caffeine or combined ingredients in many pre-workout supplements. Due to the popularity and efficacy of both ingredients, as well as their independent mechanistic

effects on exercise performance, concurrent ingestion and potential interactions have gained interest. Early research reported that CrM administered in a caffeinated beverage significantly augmented muscle creatine content [80], and the independent pharmacokinetic properties of creatine and caffeine do not appear to be altered when consumed together [81].

Creatine and caffeine have independent ergogenic mechanisms. CrM is known for its ability to increase muscle creatine storage, resulting in greater rephosphorylation of adenosine diphosphate. Whereas caffeine's positive effects on exercise are attributed to its properties as an adenosine receptor antagonist, potentiation of calcium release from the sarcoplasmic reticulum, along with peripheral effects on substrate utilization and accelerating sodium/potassium pump activity [82]. While these effects are independent, caffeine has been shown to facilitate creatine uptake by stimulating creatine transporters within the sarcolemma [83]. Specifically, caffeine may activate the sodium-potassium ATPase pump, increasing the sodium gradient along the sarcolemma. Creatine transporters rely on extracellular sodium levels, which may be stimulated by the caffeine induced sodium gradient. Thus, some have hypothesized that CrM and caffeine may result in synergistic effects. However, other evidence suggests caffeine may attenuate the ergogenic effects of CrM due to opposing effects on calcium kinetics at the sarcoplasmic reticulum [84], delaying relaxation times and, therefore, reducing exercise performance. Additionally, it has been theorized that co-ingestion of CrM and caffeine would increase symptoms of gastrointestinal distress, which could indirectly reduce performance [83,85]. Vandenberghe et al. [83] examined concomitant ingestion of CrM and caffeine and had three participants report minor gastrointestinal distress (two participants in the CrM only group and one participant in the CrM plus caffeine group). Despite the popularity and efficacy of these two ingredients there is still minimal research exploring the performance effects of co-ingestion with more recent systematic reviews describing 10 relevant studies [86,87]. Available studies have explored acute caffeine intake after CrM loading, or more chronic (>3 days) of combined caffeine and CrM. Collectively, when a single dose of caffeine is consumed acutely (5–6 mg/kg), within 60 minutes prior to exercise, after a CrM loading period (0.3 grams/kg/day for 5–6 days), there seems to be an additive effect on aerobic exercise performance more than CrM alone [87–89]. In contrast, one study to date has demonstrated no additive effect of caffeine (3 mg/kg) after 6 days of CrM loading (0.3 grams/kg/day) [90].

When evaluating chronic caffeine ingestion (300 mg/day or 5 mg/kg/day) along with CrM loading (0.5 grams/kg/day or 20 grams/day) for 3–5 days, no added benefits on maximal force [83], upper or lower body max strength [85,91], or repetitions to fatigue [85] have been reported. One study to date has explored combined ingestion of caffeine (6 mg/kg/day) and CrM (3 grams/day) for 3 days, and demonstrated improved maximal knee extension torque compared to CrM alone [92]. A similar combined dosing strategy involving CrM (20 grams/day for 4 days or 0.5 grams/kg/day for 1 day) and 5 mg/kg/day of caffeine resulted in interference between the two ingredients [83,84], and three other studies reported no effect [81,85,91]. Similarly, combining daily caffeine (300 mg or 5 mg/kg for 3–5 days) during a creatine loading period also does not seem to provide additional exercise benefits [86]. Importantly, despite the lack of effect on performance, there also do not appear to be consistent detrimental effects, thus the ingredients likely do not oppose each other, but also likely do not accelerate ergogenic effects when habitually consumed.

The potential opposing effects of caffeine with CrM are more likely influenced by doses of caffeine ≥ 5 mg/kg, as well as with individuals who have a lower tolerance to caffeine [86].

Additional considerations should be given to the increase in daily creatine use (3–10 grams/day) for benefits beyond just performance. The impact of daily caffeine intake on this daily CrM strategy has not yet been evaluated. Based on their mechanisms, CrM and caffeine likely do not oppose each other when consumed together during the short-term. However, they are also unlikely to provide additional benefits unless CrM has been taken daily long enough to saturate muscle stores, similar to a loading phase.

In summary, short-term CrM and caffeine ingestion (<5 mg/kg/day) likely does not cause opposing muscle effects. The long-term possible interference effects of CrM and caffeine are unknown. Consider acute caffeine intake after CrM loading for potential performance benefits. Chronic caffeine use, combined with CrM loading, does not result in greater exercise effects. This combined strategy may increase gastrointestinal distress and may indirectly interfere with performance.

6. Does CrM influence the rates of muscle protein synthesis or breakdown?

The benefits of CrM for increasing muscle mass during resistance training are well established (for reviews see Burke et al. [93], Chilibeck et al. [19], and Forbes and Candow [94]). These skeletal muscle benefits are likely attributable, in part, to creatine's positive influence on growth-related myogenic transcription factors, satellite cell activity and insulin-like growth-factor I [19]. However, the extent to which CrM influences measures of muscle protein kinetics remain ambiguous. Louis et al. [95] examined the effects of CrM (21 grams/day for 5 days) on the rates of muscle protein synthesis during fasted and fed states in a small group of males ($n = 6$). The authors reported that feeding significantly doubled the rates of muscle protein synthesis by 40%, but CrM did not alter these responses. The same research group also examined the effects of short-term CrM (21 grams/day for 5 days) in conjunction with single-leg resistance exercise [96]. Stable isotope techniques were used to measure myofibrillar and sarcoplasmic protein synthetic rates. The resistance exercise bout increased synthetic rates two- to threefold, but the addition of CrM did not augment these effects. Parise et al. [97] examined the effects of short-term CrM (20 grams/day for 5 days followed by 5 grams/day for another 3–4 days) in healthy young men ($n = 13$) and women ($n = 14$). In men only, CrM reduced the rate of leucine oxidation by 19.6% and decreased the rate of plasma leucine appearance (an indicator of muscle protein catabolism) by 7.5%, indicating a potential anti-catabolic effect. In healthy older men, CrM (0.1 grams/kg/day) during 10 weeks of supervised, whole-body resistance training reduced the urinary excretion of 3-methylhistidine (3-MH; an indicator of whole-body protein catabolism) by 40% compared to a 29% increase for those ingesting placebo [98]. Similarly, healthy older men supplementing with CrM (0.1 grams/kg/day) during 12 weeks of resistance training experienced a significant decrease in 3-MH. However, older women on creatine did not experience the same anti-catabolic effects [99].

In summary, a small body of research shows that CrM does not increase the rates of muscle protein synthesis. However, there is some existing evidence to support the anti-catabolic effects of CrM in men.

7. Is CrM an anti-inflammatory intervention?

There is preliminary evidence that CrM can attenuate markers of oxidative stress and the inflammatory process in humans, thereby implicating a possible anti-inflammatory role for CrM in a variety of cells and tissue types [100]. However, the mechanisms by which CrM imposes its anti-inflammatory effects are not well understood. The initial occurrence from an acute phase inflammatory response involves the increased secretion of pro-inflammatory mediators such as interleukin-8 (IL-8), tumor necrosis factor- α (TNF- α), and IL-1 β [101], and, in response to strenuous exercise, IL-6, interferon- γ (INF- γ), and C-reactive protein (CRP) have been shown to increase [102]. Strenuous exercise has also been shown to increase prostaglandin E₂ (PGE₂) instigated by muscle damage [103]. However, CrM (20 grams/day for 5 days) prior to a 3 km race attenuated increases in plasma TNF- α and PGE₂, compared to placebo, 24 hours following the race [104]. Similarly, CrM for 5 days at a dose of 20 grams/day prior to a half-ironman competition attenuated the increase in plasma levels of TNF- α , INF- γ , IL-1 β , and PGE₂ at 24- and 48-hours following the competition compared to placebo [105]. In an anaerobic exercise scenario, CrM for 7 days at a daily dose of 0.3 grams/kg prior to repeated-sprint exercise resulted in attenuations in TNF- α and CRP at 1-hour post-exercise but had no impact on the oxidative stress markers, superoxide dismutase (SOD) and catalase [106]. Furthermore, Rawson et al. [107] found no effect of 10 days of CrM (0.3 grams/kg/day) on CRP concentrations following acute resistance exercise (5 sets of 15–20 repetitions at 50% of 1-repetition maximum for the back squat exercise) in healthy resistance-trained men. Collectively, these findings suggest that CrM may be anti-inflammatory following aerobic exercise compared to resistance training; however, these results may be related to exercise volume and not exercise modality.

In summary, short-term CrM may reduce some markers of inflammation, primarily in response to aerobic-type activities. Further research is needed to determine the long-term mechanistic effects of CrM on inflammatory responses to exercise.

8. Can CrM increase recovery following injury, surgery and/or immobilization?

The potential therapeutic utility of CrM for enhancing recovery from injury, surgery and/or immobilization likely relies on its bioenergetic role as an intracellular energy buffer. In these conditions, increased creatine content may offset critical intracellular loss of energy (both in muscle and brain), facilitate the rehabilitation of disuse atrophy and accelerate functional recovery [108,109]. While these assertions seem to be supported by pre-clinical data, clinical trials, which are in their infancy, have shown mixed outcomes. Hausmann et al. [110] found protective effects of CrM in an animal model of spinal cord injury. Twenty adult rats were fed for 4 weeks with or without CrM (5 grams/100 grams of dry food) before undergoing a moderate spinal cord contusion. Rats on CrM showed better posttraumatic locomotor capacity vs. controls 1 and 2 weeks after

the injury. Furthermore, histological analysis of the lesion site showed slightly smaller scar tissue in supplemented animals, suggesting a reduced spread of secondary injury. Based on these findings, the authors concluded that CrM could be useful as a neuroprotective aid in cases of elective surgery within the spinal cord. Ozkan et al. [111] investigated the effects of CrM (300 mg/kg) vs. control on the muscle reinnervation of Wistar rats, which had the sciatic nerve experimentally denervated. Rats then had their nerves either repaired with epineural stitches or had the proximal and distal ends of the nerves ligated, with no neural anastomosis. Six months following the procedure, CrM was able to improve the functional properties of denervated muscle (which included histomorphometry and histochemical assessments) in both surgically repaired and unrepaired nerve injuries. These findings led the authors to suggest that CrM could be useful in preventing muscle wasting owing to disuse.

Despite these promising results in animal models, results from human trials are less robust. Hespel et al. [112] conducted a double-blind trial in which young healthy participants ($n = 22$) had their right leg immobilized using a plaster-cast for 2 weeks. Participants then underwent a knee-extension rehabilitation program for 10 weeks, while receiving either CrM (15 grams for the first 3 weeks followed by 5 grams for 7 weeks) or placebo. Prior to and after immobilization, and after 3 and 10 weeks of the rehabilitation stage, quadriceps cross-sectional area, isokinetic knee-extension power and myogenic transcription factors were assessed. The authors observed that CrM promoted muscle hypertrophy during rehabilitative strength training, which was possibly mediated by modulation of the myogenic regulatory factors MRF4 and myogenin expression, both being intracellular proteins that promote muscle growth or through enhanced training capacity due to greater intramuscular PCr and creatine stores. These results expand on the work by Johnston et al. [113] who showed that CrM (20 grams/day for 7 days) preserved lean tissue mass and muscle performance in young healthy adults who volunteered to have their upper limb immobilized (plaster-cast) compared to placebo. Contrary to these findings, Backx et al. [114] failed to demonstrate beneficial effects of CrM in healthy young men ($n = 30$) randomly assigned to receive either CrM (20 grams/day) or placebo for 5 days before one leg was immobilized using a cast for 7 days. Neither the immobilization-induced decrease in quadriceps cross-sectional area nor the decrease in 1-repetition maximum knee extension performance were prevented by CrM, likely suggesting inconsistency in efficacy between short- (1 week) and long-term (3 to 10 weeks) use of this supplementation strategy.

Results are also conflicting in clinical populations. In a crossover fashion, patients with complete cervical-level spinal cord injury ($n = 16$) were given CrM (20 grams/day) or placebo for 7 days. Incremental peak arm ergometry tests were performed following each condition. As compared to placebo, CrM increased VO_2max , VCO_2 , and tidal volume at peak effort, suggesting potential enhancements in exercise capacity in this population. In contrast, a randomized clinical trial of CrM (20 grams/day for the first 7 days, followed by 5 grams/day for 12 weeks) vs. placebo for patients who underwent anterior cruciate ligament reconstruction ($n = 60$) produced null findings [115]. Quadriceps and hamstring strength and power were measured by an isokinetic dynamometer prior to surgery and at 6 weeks, 12 weeks, or 6 months after surgery. Strength improvements were seen over time as result of the rehabilitation program, but CrM did not enhance the recovery beyond those found from the rehabilitation program alone.

In summary, mechanistic and pre-clinical data suggest that CrM has the potential to enhance recovery following injury, surgery, or immobilization. However, clinical data remain scarce and conflicting. Confounding factors include CrM protocol (short- or long-term), combination with other therapies (exercise rehabilitation), and type of condition (transitory vs. permanent injury; orthopedic vs. neuromuscular injury). Further, well-powered, randomized controlled trials should address these gaps.

9. Does CrM cause cancer?

A large amount of negative press claiming that CrM causes cancer emerged after a review paper summarized the potential for CrM and creatinine (a metabolic by-product of creatine metabolism) to produce mutagenic/carcinogenic compounds [116]. This paper provided an in-depth review of the literature regarding the potential for CrM and creatinine to be involved in biochemical reactions leading to the production of mutagenic compounds (heterocyclic amines) and concluded that (these compounds, not CrM *per se*), may impose only a minor health risk [116]. In brief, they highlighted the data showing that the consumption of cooked and processed meats (containing creatine and creatinine) led to the production of mutagenic compounds such as amino-imidazo-azaarenes (AIA) and that the amount was proportionate to the amount of creatine/creatinine in meat, the amount of sugar (especially fructose) and amino acids, and the cooking methods. For AIA to become carcinogenic there are a series of other metabolic reactions that must occur before they attain mutagenic (DNA guanidine adducts) potential. Nitrites are formed in the mouth and stomach from dietary nitrates and creatinine can be nitrosylated to form N-methyl-N-nitrosourea, sarcosine and N-nitrososarcosine [117,118]. Some of these nitrosylated compounds can be mutagenic in the Ames test. There is a positive correlation between dietary nitrate/nitrite intake and mortality from gastric cancer mortality, with a lowering of gastric cancer incidence in the United States, co-temporal with a reduction in gastric nitrate/nitrite load from 1925 to 1981 [119,120]. Collectively, this body of literature supports the recommendation that people should limit the consumption of highly processed, overcooked (very prolonged cooking, blackened [i.e. barbeque; BBQ] flesh containing creatine and creatinine [meat, fish]). Interestingly, when pigs were fed high doses of CrM (50 grams/day), there was no increase in the levels of heterocyclic amines in the meat from supplemented vs non-supplemented animals [121]. Importantly, there is no evidence that CrM at typical recommended levels (i.e. 3–5 grams/day) would lead to the production of such carcinogenic compounds without simultaneously being exposed to high temperatures, amino acids, nitrites and sugars. Indeed, CrM at 7 grams/day for 7 days followed by ≤ 5 grams/day for 23 days does not lead to an increase in carcinogenic heterocyclic amines in young males and females [122]; an epidemiological study in > 7000 men and women found that a lower dietary creatine intake was associated with a slightly higher risk of cancer (which remained after controlling for moderate physical activity and other lifestyle factors) [123]; and most pre-clinical studies showing *in vivo* carcinogenesis used heterocyclic amines at much higher amounts than those found in cooked/processed meats.

A second “peak” in the speculation that CrM causes cancer resulted from a paper looking at cancer metastasis in a murine (rodent) model and concluded that CrM in cancer survivors promotes cancer metastasis [124]. In brief, this study

found that cancer cells upregulate glycine amidino transferase (*GATM*) expression to increase intra-cellular creatine production and that blocking this up-regulation attenuated metastasis. They also found that CrM (5 % wet-weight; w/w) did not alter primary colonic tumor growth (and even mildly suppressed it) but enhanced the metastases to the liver [124]. There are several caveats to this study including that the 5 % w/w CrM supplement dose used is equivalent to ~28 grams of CrM/day in humans or 5–9 times the typical recommended CrM long-term dose of 3–5 grams/day. Secondly, the metastases were in the liver and liver inflammation appears to be a species specific side effect of CrM in mice but not in rats or humans [125]. Furthermore, it is clear that cancer cells are voracious consumers of energy and promiscuous in terms of the type of energy source needed to support rapid growth and metastasis. The Warburg effect is a cancer cell specific upregulation of glycolytic flux that increases the flux of carbon from glucose to 3-phosphoglycerate toward DNA synthesis through the serine-glycine-one carbon (SGOC) pathway [126]. Due to the high energetic demand from rapidly growing tumor cells, it is also not surprising that many tumor cells express high level of cytosolic creatine kinase (CK-BB) [127], and ubiquitous mitochondrial CK (CKMT1) [128,129]. In fact, this phenomenon was targeted using cyclocreatine to block the reaction and attenuate energy transduction and hence carcinogenesis in several studies [130,131]. Another complicating issue is that tumor cells can alter aspects of creatine metabolism when they transition from primary tumors to metastatic tumors with the former expressing high levels of CKMT1 and the latter showing down-regulation [129]. The down-regulation of CKMT1 is associated with higher levels of reactive oxygen species that promote metastasis dependent expression of adhesion and matrix degradation proteins that are protected using anti-oxidants [129]. As a consequence of the high metabolic demand of cancer cells, the changing dynamics of metabolism between and within different types of cancer cells as they transition from a primary to a metastatic cancer makes conclusions about when a metabolic substrate could be deleterious, neutral or beneficial to a patient with a primary or metastatic tumor very complicated. Indeed, other studies have shown that creatine does not promote tumor growth or proliferation [132], or is protective in some cancer models [133–135], possibly by up-regulating the energy supply to anti-cancer T-cells [133,136].

A final consideration regarding CrM and cancer comes from the strong evidence that CrM can protect against several deleterious health consequences from tumor (i.e. cancer cachexia) and/or the treatment (i.e. chemotherapy). Cancer cachexia refers to the loss of lean tissue mass in response to the flux of energy to the growing tumor, lower energy intake due to the tumor and/or chemotherapy and in response to cytokines that alter metabolism and appetite. Given the well established benefits of CrM on measures of lean tissue mass and performance [137–140], it is not surprising that several studies are planned to evaluate the benefits of exercise training and CrM in cancer survivors [141–143]. Many studies have shown the benefits of CrM with or without exercise training to attenuate the deleterious effects of chemotherapy (doxorubicin) upon lean tissue mass and function [144–148], and one study found that children treated with prednisone for acute lymphoblastic leukemia had lower body fat when supplemented with CrM [149].

In summary, evidence-based research does not support that CrM (3–5 grams/day) in humans increases the formation of carcinogenic compounds or cancer risk (primary or metastasis). It is likely to be beneficial to help protect and/or recover from the skeletal muscle and body composition issues associated with cancer per se and/or the effects of chemotherapy. It is prudent to limit the intake of highly processed and/or overcooked meats/fish (i.e. BBQ) to lower the risk of gastric cancers.

10. Will CrM increase urine production?

Urine production is a finely regulated process primarily controlled by the kidneys through intricate mechanisms involving filtration, reabsorption, and secretion [150]. Key factors influencing urine production include the glomerular filtration rate (GFR), hormonal regulation, fluid intake, solute load, and renal perfusion pressure. These factors collectively determine the volume and concentration of urine produced by the body to maintain fluid and electrolyte balance [150]. One common misconception is that CrM directly leads to increased urine production. However, scientific evidence (though very few studies use urine volume as a primary outcome variable) suggests that it is not CrM that causes a rise in urine production but rather the associated increase in water or fluid intake often consumed at the same time with CrM, typically in conjunction with exercise training. Kreider et al. [151] examined 98 Division IA college football players' urine output during a 21-month period of CrM. Compared to placebo, CrM resulted in similar urine outcome variables over time. Increased fluid intake, often encouraged alongside CrM, is likely the main reason urine production increased. When more fluids are consumed, the kidneys upregulate GFR activity to maintain the body's fluid and electrolyte balance by filtering the excess water out of the bloodstream and into the urine [150]. This process is regulated by antidiuretic hormone (ADH), which controls the amount of water reabsorbed by the kidneys. Higher fluid intake reduces ADH levels, leading to less water reabsorption and consequently, increased urine production. This physiological response tightly regulates fluid homeostasis, resulting in more frequent urination. It is important to note that creatine is efficiently metabolized by the body, with daily intake and excretion being approximately equal [152]. Therefore, the idea that CrM itself leads to a significant increase in urine production is unfounded and not supported by scientific evidence.

In summary, while CrM may result in higher fluid intake, leading to increased urine production, CrM itself does not independently drive changes in urine volume.

11. Does CrM influence blood pressure?

There has been speculation that CrM might increase blood pressure due to a number of factors, including fluid retention within cells and increased stress on kidney function. In addition, creatine kinase, the enzyme involved in the process by which PCr rephosphorylates ADP to ATP is high in resistance arteries and may be involved with vasoconstriction to increase blood pressure [153]. Serum creatine kinase, as a surrogate for tissue creatine kinase, is associated with increased blood pressure [153]; however, the concentration of this enzyme in blood is not a direct indication of creatine concentration in tissue, but rather an indication of plasma membrane damage (majority coming from skeletal muscle). Despite these concerns, relatively high-dose (i.e. 10–20 grams/day) but

short term (i.e. 5–31 days) CrM in young, healthy males and females did not affect blood pressure [154–156]. Most importantly, a systematic review of clinical populations (i.e. patients with heart failure, ischemic heart disease, or myocardial infarction) found no impact of CrM (again at relatively high doses, i.e. 20 grams/day for up to 6 weeks) on blood pressure [157]. In a recent two-year intervention (which focused on changes in bone), postmenopausal women (mean age ~59 years) were randomized to receive a relatively high dose of CrM (0.14 grams/kg/day) or placebo [158] and participants at one of the research sites had blood pressure measured before and after the intervention. For those who completed the intervention ($n = 60$ on CrM, $n = 52$ on placebo) there was no difference between groups for changes in either systolic (CrM = 121 ± 15 to 124 ± 11 mmHg; placebo = 116 ± 13 to 121 ± 15 mmHg; $p = 0.34$) or diastolic (CrM = 77 ± 8 to 76 ± 7 mmHg; placebo = 75 ± 8 to 76 ± 9 mmHg; $p = 0.65$) blood pressure. Studies of CrM in people who were hypertensive at baseline are missing from the literature; however, one study in spontaneously hypertensive rats found no effect of CrM (5 grams/kg/day for 9 weeks) on blood pressure [159]. Finally, there is some research indicating CrM might be effective for reducing the blood pressure response to a resistance-training session: Three weeks of CrM (10 grams/day) in young males reduced the acute blood pressure response to resistance-training compared to placebo [160]. It was speculated that an improvement in anaerobic metabolism with CrM would attenuate production of metabolic by-products such as lactate or ammonia, which might stimulate muscle metaboreceptors involved in activation of the sympathetic nervous system [160].

In summary, there is no evidence that short-term or chronic CrM adversely affects blood pressure.

12. Is CrM safe to consume during pregnancy?

Regulation of creatine metabolism may be important in all aspects of reproduction, from fertilization to pregnancy and fetal growth [161–167], labor and birth [168], breastfeeding [169], and early childhood development [170]. This increasing body of research is raising questions about optimal dietary creatine intake during pregnancy and whether CrM may benefit certain populations [171,172], including infants born preterm [173]. In particular, studies are ongoing to explore the potential of CrM during pregnancy to increase fetal creatine reserves and support energy homeostasis during periods of mild to severe hypoxia-ischemia, potentially preventing major complications like perinatal hypoxic-ischemic encephalopathy (HIE). Initial findings from pre-clinical models have been promising [174]. An interesting aspect of CrM for improving newborn outcomes is its use as a prophylactic agent in high-risk pregnancies [175]. This approach addresses the challenge of identifying pregnancies at risk of acute hypoxic events [176]. However, it does raise questions about potentially exposing healthy fetuses to high creatine concentrations throughout the antenatal period [177].

Generating data on the safety of CrM during pregnancy, in addition to establishing its efficacy, has been integrated into the design of recent pre-clinical animal studies. In the spiny mouse model of intrapartum hypoxia, where pregnant dams were fed a 5% w/w CrM from mid-gestation until delivery (a period of 18 days) [178], offspring exposed to increased levels of creatine *in utero* were followed through to adulthood with no reported impact on body growth, renal, skeletal muscle or diaphragm structure or function [179–181]. In

addition, a study conducted in non-pregnant and pregnant spiny mice focused on the impact of CrM on maternal creatine homeostasis, body composition, capacity for *de novo* creatine synthesis and renal excretory function found no sustained negative impacts on maternal physiology [182]. Comprehensive data on fetal well-being has also been reported from chronically instrumented fetal sheep supplemented with a continuous intravenous infusion of $6 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ of CrM for 13 days at the cerebral development equivalent gestational age of 34 to 36 weeks of human pregnancy. The 5-fold increased circulating creatine concentrations achieved with direct fetal supplementation had no impact on cardiovascular or systemic arterial blood gas parameters throughout the supplementation period and no change in fetal body or organ weights at postmortem [183]. This CrM regime also did not negatively impact cerebral interstitial concentrations of lactate, glutamate or hydroxy free radicals in the near-term fetal brain [184]. At a cellular level, *in utero* creatine exposure was linked to transcriptional changes in genes associated with anti-apoptotic pathways and mitogenesis, particularly in the fetal hippocampus, but this was not directly linked to any changes in cell death, mitochondrial respiration or mitochondrial complex density [185]. Changes in genes associated with innate immunity in the cortical gray matter and striatum have also been noted, including an upregulation of major inflammatory mediators including IL-6, IL-1 β , TNF α , and prostaglandin synthase. Whether these changes indicate CrM produces a pro-inflammatory environment is yet to be ascertained. However, the same study did not observe increases in the presence of microglia and astrocytes nor increased markers of oxidative stress at a protein level [185,186]. Of note, increased myelin basic protein immuno-positive area coverage in the subcortical white matter observed in fetal sheep indicate a potential for *in utero* CrM to enhance or speed up myelination in the developing brain. A similar finding has been reported in male rat pups born to dams supplemented with 1% CrM in their drinking water for the final 10 days of pregnancy. Electrophysiological recordings from hippocampal pyramidal neurons of these rat pups at postnatal day 14–21 displayed increased excitability and enhanced long-term potentiation, despite increased creatine exposure being ceased at birth [187]. In follow-up assessments, these neurological changes observed in young rats persisted, suggesting improved synaptic plasticity into adulthood [188]. While the subtle changes observed in the brain following *in utero* creatine exposure to date do not suggest a negative impact on offspring welfare or cognitive abilities, it remains important to thoroughly characterize any shift in neurodevelopment brought about by CrM during pregnancy with continued pre-clinical evaluation.

The translation of CrM as a pregnancy intervention is still in its infancy, with initial pharmacokinetic and tolerability studies underway (ACTRN:12620001373965). As such, there is currently no direct evidence available from well-designed and executed randomized controlled clinical trials (RCTs) on the safety and tolerability of CrM during human pregnancy. However, a recent systematic review and meta-analysis of CrM in female-only populations of reproductive age assessed the safety outcomes [189]. This study reviewed the data from 29 studies that collectively consented 951 participants ranging from 16 to 67 years of age that received 1–30 grams of CrM per day for between 4 days to 365 days. No deaths or serious adverse events (defined as any outcome that causes life-threatening events; requirement for hospitalization or prolongation of existing hospitalization; persistent or significant disability; or any events considered medically important) were reported in any of the trials reviewed. When stratified by dosing regimens, meta-analyses confirmed that there were also no significant differences in minor adverse events between

CrM and control groups, including gastrointestinal events, blood and urine biomarkers of renal and hepatic function, or weight gain.

In summary, preliminary research involving animal models suggest that CrM during pregnancy does not negatively affect the mother or offspring. However, there is currently no direct evidence available from well-designed and executed randomized controlled clinical trials on the safety and tolerability of CrM during human pregnancy.

13. Does CrM enhance performance in adolescents?

In conjunction with the substantial amount of evidence that supports the performance-enhancing abilities of CrM for various adult populations [8,190,191], the body of scientific literature regarding the benefits of CrM for children and adolescents continues to grow (Table 1). To date, many of the studies involving adolescents have focused on swimming and soccer performance [202,203]. Most studies employed a short-term (4–7 days) CrM loading dose of 20–25 grams/day, followed by a CrM maintenance dose of 5 grams/day. Grindstaff et al. [193] were one of the first to evaluate the effects of CrM on sport-specific performance in adolescent male swimmers and reported significant improvements in sprint swimming performance after nine days of CrM at a daily dose of 21 grams. In a similar study, Juhasz et al. [194] reported significant improvements in power output and 100 m sprint swimming performance following CrM (20 grams for 5 days) in elite junior male swimmers.

For soccer-specific performance, Mohebbi et al. [198] reported improvements in repeat sprint performance and dribbling performance after seven days of CrM supplementation (20 grams/day) in adolescent male soccer players. Similarly, Ostojic et al. [199] reported improvements in dribble test and endurance times along with improvements in sprint power and countermovement jump performance following seven days of CrM (30 grams/day) in adolescent male soccer players.

Research has also explored alternative applications of CrM beyond direct measures of sports performance. For example, Ojeda et al. [201] recently reported that CrM (0.3 grams/kg/day for 14 days) led to an improved ability to maintain muscle power following the induction of intrasession fatigue in young (17 years of age) male soccer players. Additionally, Juhasz et al. [204] observed greater improvements in segmental lean mass and plantar flexion torque following limb immobilization in adolescent swimmers recovering from tendon overuse injuries after CrM (20 grams/day for 5 days followed by 5 grams/day for 37 days).

In summary, CrM can improve measures of sports-specific activities as well as similar indices of physical performance such as power or sprint speed in adolescents. Research in female adolescent athlete populations is significantly lacking. Long-term RCT's designed to examine changes in training adaptations in adolescent populations from CrM are needed.

14. Does CrM adversely affect male fertility?

The notion of CrM having detrimental effects on male fertility seems to be propagated by dubious sources. This speculation often stems from studies involving multi-component bodybuilding supplements that contain various ingredients, including anabolic steroids,

Table 1. Summary of the effects of creatine supplementation in adolescents.

Author Year (Country)	Subjects	Study Design	Duration	Dosing Protocol	Primary Variables	Results	Adverse Events
<i>Swimming</i> Dawson et al. [192] (Australia)	10 males, 10 females (16.4 ± 1.8 years)	Matched, placebo-controlled	4 weeks	20 g/day (5 days) 5 g/day (22 days)	Sprint swim performance and swim bench test	↑ swim bench test performance	None reported
Grindstaff et al. [193] (USA)	18 (11 F, 7 M) adolescent swimmers (15.3 ± 0.6 years)	Randomized, double-blind, placebo controlled	9 days	21 g/day	Sprint swim performance; arm ergometer performance	↑ sprint swimming performance	None reported
Juhász et al. [194] (Hungary)	16 male fin swimmers (15.9 ± 1.6 years)	Randomized, placebo-controlled, single-blind	5 days	20 g/day	Average power, dynamic strength (swim based tests)	↑ anaerobic performance ↑ dynamic strength	None reported
Theodorou et al. [195] (United Kingdom)	10 elite female (17.7 ± 2.0 years) and 12 elite male (17.7 ± 2.3 years) swimmers	Randomized, double-blind, placebo-controlled	11 weeks	25 g/day (4 days) 5 g/day (2 months)	Swimming interval performance	↑ interval performance following loading phase ↔ long-term improvements after maintenance dose	None reported
Theodorou et al. [196] (United Kingdom)	10 swimmers (6 M, 4F) (17.8 ± 1.8 years)	Randomized, double-blind trial	4 days	20 g/day of CrM or 20 g/day of CrM + 100 g of carbohydrates per serving	High-intensity swim performance during repeated intervals	↑ mean swim velocity for all swimmers ↔ swim velocity in Cr + Carbohydrate condition	Gastrointestinal discomfort in Cr + Carbohydrate group only
<i>Soccer</i> Claudino et al. [197] (Brazil)	14 male elite soccer players (18.3 ± 0.9 years, 69.9 ± 8.8 kg)	Randomized, double-blind, placebo-controlled	7 weeks	20 g/day (1 week) 5 g/day (6 weeks)	Lower limb muscle power via countermovement vertical jump	↔ lower body power	None reported
Mohebbi et al. [198] (Iran)	17 soccer players (17.2 ± 1.4 years, 61.7 ± 1.4 kg)	Randomized, double-blind, placebo-controlled	7 days	20 g/day	Repeated sprint test, soccer dribbling performance and shooting accuracy	↑ repeat sprint performance ↑ dribbling performance	None reported
Ostojic et al. [199] (Yugoslavia)	20 male soccer players (16.6 ± 1.9 years, 63.6 ± 5.6 kg)	Matched, placebo-controlled	7 days	30 g/day	Soccer specific skills tests	↑ dribble test and endurance times ↑ sprint power test and countermovement jump	None reported

(Continued)

Table 1. (Continued).

Author Year (Country)	Subjects	Study Design	Duration	Dosing Protocol	Primary Variables	Results	Adverse Events
Yanez-Silva et al. [200] (Brazil)	19 male soccer players (17.0 ± 0.5 years, 66.8 ± 3.2 kg)	Matched, double-blind, placebo- controlled	7 days	0.03 g/kg/day	Muscle power output (Wingate anaerobic power test)	↑ peak and mean power output ↑ total work	None reported
Ojeda et al. [201] (Chile)	28 male soccer players (17.1 ± 0.9 years, 68.5 ± 6.0 kg)	Randomized, double-blind, placebo- controlled	14 days	0.3 g/kg/day	Muscle power assessed after fatigue induction	↑ in bar velocity and power in creatine group led to significant differences between groups after supplementation.	No

↔ = Creatine supplementation resulted in no significant ($p < 0.05$) change; ↑ = Creatine supplementation resulted in a significant increase ($p < 0.05$) over control. CrM = creatine monohydrate; g/day = grams per day. Adapted from Jagim et al. [202].

which can potentially impair sperm function [205,206]. Furthermore, anecdotal claims in public media suggest that CrM may induce dehydration, leading to impaired sperm production and function, or elevate testosterone levels, which could negatively impact male fertility. However, contrary to these claims, CrM actually improves water retention [207], and the majority of studies indicate that it has no effect on testosterone levels (for an in-depth review, see Antonio et al., [10]). Hence, the anecdotal claims regarding the harmful effects of CrM on male fertility lack validity.

Creatine may play a significant role in sperm viability. Semen, being a high-energy-demanding fluid, exhibits relatively high creatine content in both spermatozoa and seminal plasma (up to 15 mm) [208], comparable to levels found in other energy-demanding cells. The testes express a unique tissue-specific membrane transport protein for creatine (CT2) [209], underscoring the importance of creatine utilization for male reproductive bioenergetics. Several preclinical and clinical studies have demonstrated that low semen creatine levels are associated with reduced sperm quality (for a detailed review, see Ostojic et al., [210]). This suggests that restoring normal creatine homeostasis in spermatozoa, possibly through CrM, could be a potential target for improving sperm quality.

Preliminary studies indicate that creatine may enhance human sperm viability. Incubating semen or migrated sperm fractions with creatine phosphate has shown to significantly improve sperm motility and velocity in normospermic donors [161]. These effects occur rapidly, with full improvements in sperm velocity and motility achieved within one minute. The authors suggest that adding creatine phosphate to insemination media could enhance the fertilizing capacity of sperm during *in vitro* fertilization or gamete intrafallopian transfer procedures. Animal studies support these findings, demonstrating the beneficial effects of creatine and creatine analogs on sperm capacitation in mice [211], fertilization ability in boars [212], and semen quality and fertility in broiler breeder roosters [213]. However, no effects of creatine on *in vitro* capacitation-related events were found in frozen equine sperm [214]. An intriguing cross-sectional study suggests that semen concentration and total sperm count may tend to be higher in healthy men who currently consume protein supplements (with 44% reporting CrM use or creatine-protein combinations) compared to former users and never users [215]. Currently, there are no human studies available investigating the effects of CrM on indices of male fertility in normospermic and/or oligospermic men.

In summary, existing evidence does not suggest that CrM negatively impacts male fertility. In fact, preliminary findings indicate that exposure to creatine may improve human sperm motility and velocity in normospermic men under in vitro conditions.

15. Does the brain require a higher dose of CrM than skeletal muscle?

The optimal dose and requirements for CrM may differ between skeletal muscle and brain tissue [216,217]. There is a well-established body of literature examining the effects of various dosages of CrM on skeletal muscle uptake and retention (for review see [140,216]). Pioneering work in the early 1990's by Drs. Roger Harris and Eric Hultman demonstrated that ingesting 20 grams/day of CrM separated into four equal doses was able to elevate intramuscular creatine stores ~ 18% within 6 days, which was maintained with 2 grams/day [3,218]. Furthermore, a much lower dose of CrM (3 grams/day) was able to elevate

creatine stores to a similar degree after 28 days of supplementation compared to the CrM loading phase (20 grams/day for 6 days). Importantly, CrM elevates plasma creatine (5 gram dose = >500 mmol/L increase), which can then be taken up into energetically demanding tissues (e.g. muscle and brain) against a concentration gradient via a sodium-chloride creatine-specific transporter protein (SLC6A8) [40,116]. Creatine transport into cells is both sodium and insulin-dependent [219]. Several studies from Dr. Paul Greenhaff's laboratory have shown that insulin augments creatine uptake into muscle and that CrM co-ingestion with either carbohydrates or protein (which both are insulinogenic) results in greater intramuscular creatine retention in the short-term [49,54,219].

In contrast to skeletal muscle, there is less evidence and understanding regarding the optimal CrM dosing protocol to increase brain creatine levels [216]. A few studies have shown that high-dose CrM (acute ingestion of 0.35 grams/kg; ≥ 20 grams/day or 0.3 grams/kg/day for at least 7 days) or lower-dose CrM (4–5 grams/day for several months) can increase total brain creatine levels in young and older adults [220–224], while others have found no effect after 7 days with ~ 20 grams/day [225]. Importantly, CrM increases brain creatine levels by ~ 5 –10% compared to a ~ 20 –40% increase in skeletal muscle [217,226]. These divergent responses may be associated with the endogenous synthesis of creatine in the brain, lack of creatine transport kinetics at the blood-brain barrier, and dosage and duration of CrM [217]. Skeletal muscle relies solely on exogenous creatine (i.e. dietary creatine and creatine synthesized in the liver), while the brain has the ability for *de novo* synthesis. The synthetic pathway involves three amino acids: arginine, glycine, and methionine and two enzymes: L-arginine: glycine amidinotransferase (AGAT) and guanidinoacetate methyltransferase (GAMT). The brain appears to rely on its own creatine synthesis under normal resting conditions. For example, CrM does not alter brain energetics or cognition in young, healthy adults, even with higher doses (e.g. 20 grams/day for 6 weeks) [227]. Further, the capacity to uptake creatine from the blood appears to be limited due to a small number, or lack thereof, of SLC6A8 transporters at the blood-brain barrier [228]. There is speculation that the brain does not necessarily rely on circulating creatine to maintain homeostasis, therefore higher doses of CrM over longer periods might be required to elevate brain creatine levels. However, this concept remains to be elucidated as previous creatine trials fail to demonstrate a dose and/or duration response relationship. For example, adolescent females on medication for major depressive disorder supplemented with either 2, 4, or 10 grams/day of CrM or placebo for 8 weeks [229]. Mean frontal lobe phosphocreatine increased by 4.6, 4.1, and 9.1% in the 2, 4, and 10 grams/day of CrM groups, respectively. Since there were no differences in the 2 and 4 grams/day of CrM groups, there does not appear to be any clear linear response, however the higher dose CrM group (10 grams/day) experienced twice the increase in brain creatine stores. Furthermore, Dechent et al. [221] had participants ingest 20 grams/day of CrM for 4 weeks and monitored brain creatine levels on a weekly basis. Results showed that total brain creatine levels increased early in the CrM period, decreased in week 3, and then increased again in week 4. Solis et al. [225] found that CrM (0.3 grams/kg/day for 7 days) did not alter brain creatine levels in young or older adults. Overall, these findings are challenging to interpret, but highlight that there is no clear dose-time relationship regarding CrM and brain creatine levels.

In summary, it is unclear whether the brain requires higher doses of CrM compared to skeletal muscle. It is well-established that a wide range of CrM protocols (20 grams/day with and without a maintenance dose, 3–5 grams/day) can increase skeletal muscle creatine stores. There is some evidence that different CrM dosing protocols (acute ingestion of 0.35 grams/kg; ≥ 20 grams/day or 0.3 grams/kg/day for at least 7 days) or lower-dose CrM (4–5 grams/day for several months) can increase brain creatine levels. However, a CrM dose and time-response relationship (if any) remains to be determined.

16. Can CrM attenuate symptoms of sleep deprivation?

Lack of sleep adversely affects cognitive function, motor skills, and mood, partly because of reduced creatine levels in the brain. Hence, it has been posited that CrM could alleviate these detrimental effects of sleep deprivation [220,226]. Nevertheless, there is a scarcity of data on the effects of CrM on sleep. McMorris et al. [230] assessed the effects of CrM, sleep deprivation, and mild exercise on cognitive and psychomotor performance, mood, and plasma concentrations of catecholamines and cortisol. In this double-blind, placebo-controlled trial, research participants (21 years of age) consumed 5 grams of CrM or placebo four times daily for one week. Participants underwent various tests including random movement generation (RMG), verbal and spatial recall, choice reaction time, static balance, and mood assessment at baseline (0 h) and after 6, 12, and 24 hours of sleep deprivation, interspersed with intermittent exercise. Blood samples were collected at 0 and 24 hours to measure plasma concentrations of catecholamines and cortisol. Results revealed that after 24 hours, the CrM group exhibited significantly less deterioration in RMG, choice reaction time, balance, and mood compared to baseline. However, there were no significant differences between groups in terms of plasma catecholamines and cortisol concentrations. In a subsequent study by McMorris et al. [231], they discovered that in the context of moderate-intensity exercise during sleep deprivation, CrM (i.e. 20 grams/day for 7 days) influenced the performance of intricate central executive tasks during 36 hours of sleep deprivation in young males (21 years of age). Furthermore, Cook et al. [232] explored how sleep deprivation, with or without the immediate intake of caffeine or CrM, affected performance during a repetitive rugby passing skill [232]. Ten top-tier rugby athletes (21 years of age) underwent 10 trials of a basic rugby passing skill test (i.e. 20 repetitions per trial) after becoming accustomed to the task. During 5 trials, participants slept between 7–9 hours, while during the other 5 trials, they experienced sleep deprivation, sleeping only 3–5 hours. Prior to each trial, participants received either: placebo pills, 50 or 100 mg/kg of CrM, or 1 or 5 mg/kg of caffeine. Saliva samples were collected before each trial and analyzed for levels of salivary free cortisol and testosterone. The CrM dose would be equivalent to 3.75–7.50 grams of CrM for a 75-kilogram individual. Sleep deprivation under the placebo condition led to a substantial decline in skill performance accuracy on both the dominant and non-dominant passing sides. However, there was no decline in skill performance observed with caffeine doses of 1 or 5 mg/kg, and there was no significant difference in the effects between these two doses. Similarly, no impairment was observed with CrM at doses of 50 or 100 mg/kg, and there was no significant difference in the performance effects between these two doses. Salivary testosterone levels were unaffected by sleep deprivation. Thus, CrM appears to

ameliorate the effects of sleep deprivation [232]. In an intriguing investigation by Gordji-Nejad et al. [222], participants (23 years of age) were orally administered a high single dose of CrM (0.35 g/kg) while performing cognitive tests during 21 hours of sleep deprivation. Results showed that a high single dose of CrM can partially reverse metabolic alterations and fatigue-related cognitive deterioration [222]. In contrast, Rawson et al. [233] found no beneficial effects from CrM (0.03 grams/kg/day) on measures of cognitive processing in young adults (21 years of age) who were not sleep-deprived [233].

In summary, preliminary evidence suggests that CrM may have a positive effect on cognitive processing under conditions of sleep deprivation in young adults. However, there is no evidence that creatine supplementation improves cognition under conditions of adequate sleep.

17. Will CrM reduce the severity of or improve recovery from traumatic brain injury?

It is becoming more widely known that increasing brain creatine through CrM improves aspects of brain health, such as cognitive processing, under both resting and especially under stressed (e.g. disease, sleep deprivation, etc.) conditions (reviewed in [217,220,234]). Traumatic brain injury (TBI) represents a unique challenge to brain health, but there is some evidence that CrM may be of benefit. Following TBI, there is increased energy need coupled with decreased energy availability, including reduced brain creatine [235,236], which creates a cellular energy crisis. In addition to the potential of CrM to help mitigate the energy drain created by brain injury, CrM may positively impact other features of TBI including: membrane disruption leading to calcium influx, nerve damage, mitochondrial dysfunction, oxidative stress, and inflammation (reviewed in [237]).

Animal models have been used to examine the ability of CrM to serve as a prophylactic nutrient to moderate the damage of TBI. Sullivan et al. [238] reported that 3 or 5 days of prophylactic creatine ingestion (3 mg/gram/day) reduced cortical damage 21% and 36%, respectively, in mice following an experimentally induced TBI. Similarly, rats fed a creatine-enriched diet prior to experimentally induced TBI demonstrated a 50% reduction in cortical damage. It is, however, difficult to study the preventative effects of CrM on TBI in humans, as concussing research volunteers is unethical and identifying concussed volunteers cannot happen until after the injury. The effects of post-brain injury CrM in children have been studied by Sakellaris et al. [239–241]. Reportedly, 6 months of CrM (0.4 grams/kg/day) in children and adolescents ($n = 39$: 1–18 years of age) with a TBI revealed many benefits, including decreased duration of post-traumatic amnesia, intubation time, and intensive care unit stay; and improved disability, recovery, self-care, communication, locomotion, sociability, personality and behavior, and neuro-physical and cognitive function [239,240]. CrM improved post-traumatic headaches, dizziness and fatigue, commonly reported as lingering problems of TBI. Dysregulation in brain energy metabolism following TBI needs further study, as TBI-related changes in brain metabolites are influenced by brain region and time [242]. Compelling data from Alosco and colleagues [243] showed that persistent, longer-term changes to cognitive, behavioral, and mood symptoms are related to reduced brain creatine in retired players from the National Football League (aged 40 to 69 years) who had experienced repetitive head impacts years earlier during their career. Furthermore, several RCT's designed to investigate the potential benefits of

CrM on recovery from TBI are currently underway (see [244], Clinicaltrials.gov ID NCT06208813, NCT05562232, NCT0558906). Additionally, a recent review by Ostojic et al. (20024) found that increased dietary creatine intake was associated with reduced circulating levels of neurofilament light chain levels, which is a common marker of neuronal damage in humans. Therefore, dietary creatine intake may exert protective effects of future neuronal injury [245].

In summary, the small body of research to date involving animal and patient populations suggest that CrM can potentially reduce severity of and/or improve recovery from TBI. In lieu of data from large RCT's, for best practice, the totality of evidence suggests that CrM for individuals at high-risk of TBI, such as athletes and military personnel, is sensible.

18. Conclusions

Based on our scientific evaluation of the literature, we conclude that:

- (1) CrM may provide benefits to skeletal muscle without exercise. Populations with lower baseline creatine levels, such as vegans and vegetarians, may experience a greater response to CrM.
- (2) The timing of CrM does not appear to be a limiting factor on the ergogenic effects of exercise training adaptations. Consistent CrM during an exercise training program is likely the most important variable.
- (3) The co-ingestion of CrM with other compounds (i.e. carbohydrates, protein) may accelerate the increase in muscle creatine levels and improve exercise performance.
- (4) Short-term creatine and caffeine ingestion (<5 mg/kg/day) likely do not cause opposing effects. Consider acute caffeine intake after CrM loading for potential performance benefits. Chronic caffeine use, combined with CrM does not result in greater exercise effects. This combined strategy may increase gastrointestinal distress and may indirectly interfere with performance.
- (5) CrM does not increase the rates of muscle protein synthesis. However, there is some existing evidence to support the anti-catabolic effects of CrM in men).
- (6) CrM changes some inflammatory markers following long-duration aerobic type exercise.
- (7) CrM has the potential to enhance the recovery following injury, surgery or immobilization.
- (8) Evidence-based research does not support that CrM in humans (3–5 grams/day) increases the formation of carcinogenic compounds or cancer risk (primary or metastasis). CrM is likely to be beneficial to help protect and/or recover from the skeletal muscle and body composition issues associated with cancer per se and/or the effects of chemotherapy.
- (9) CrM does not increase urine production.
- (10) There is no evidence that CrM adversely affects blood pressure parameters.
- (11) Animal research suggests that CrM during pregnancy does not negatively impact the mother or offspring. However, there are no well-designed or executed

randomized controlled clinical trials on the safety and tolerability of CrM during human pregnancy.

- (12) In adolescents, CrM can improve measures of sports-specific activities in addition to improving power or sprint speed in adolescents.
- (13) CrM does not negatively impact male fertility.
- (14) It is unclear whether the brain requires more CrM than skeletal muscle to increase creatine levels.
- (15) CrM may positively affect cognition and memory during periods of sleep deprivation in young adults, but not for those with adequate sleep.
- (16) CrM has the potential to reduce the severity of and/or improve recovery from TBI.

Disclosure statement

JA: is the CEO and co-founder of the International Society of Sports Nutrition, an academic non-profit. The ISSN may be sponsored by companies that manufacture, market, and sell creatine-containing supplements, including Creapure, Bear Balanced, and Create.

DGC: has conducted industry-sponsored research involving creatine supplementation and received creatine donations for scientific studies and travel support for presentations involving creatine supplementation at scientific conferences. In addition, D.G.C. serves on the Scientific Advisory Board for Alzchem and Create (companies that manufacture creatine products) and as an expert witness/consultant in legal cases involving creatine supplementation.

SJE: serves on the Scientific Advisory Board of Alzchem.

SCF: previously served as a scientific advisor for a company that sold creatine; has received creatine donations for scientific studies; sold creatine education resources; and is a sports nutrition advisor for the International Society of Sports Nutrition (ISSN); is a scientific advisor for Bear Balanced (a company which manufactures creatine products).

BG: has received research grants, creatine donation for scientific studies, travel support for participation in scientific conferences, and honorarium for speaking at lectures from AlzChem (a company which manufactures creatine). Additionally, he serves as a member of the Scientific Advisory Board for Alzchem.

ARJ and CMK: have consulted with and received external funding from companies that sell certain dietary ingredients and have received remuneration from companies for delivering scientific presentations at conferences. ARJ writes for online and other media outlets on topics related to exercise and nutrition. In addition, ARJ serves on the Scientific Advisory Board for Alzchem.

RBK: has conducted sponsored research, received honorarium for presenting research, served as a scientific expert, and consulted with industry on product development related to creatine supplementation. He serves as Chair of the Creatine for Health Scientific Advisory sponsored by Alzchem.

SMO: serves as members of the Scientific Advisory Board on creatine in health and medicine (AlzChem LLC). SMO co-owns patent "Supplements Based on Liquid Creatine" at European Patent Office (WO2019150323 A1). SMO has received research support related to creatine during the past 36 months from the Ministry of Education, Science, and Technological Development; Provincial Secretariat for Higher Education and Scientific Research; Alzchem Group AG; ThermoLife International; and Hueston Hennigan LLP. SMO does not own stocks and shares in any organization.

MDR: has performed industry- and commodity-based contract work, with recent support being received by the US National Dairy Council, The US Peanut Institute, The Center for Applied Health Sciences, MegaFood, and a three-year laboratory donation from Nutrabolt. MDR also performs consulting for personal fees with industry partners in accordance with Auburn University's faculty consulting and annual disclosure policies. MDR has no associated creatine grants to support.

ESR: has conducted industry sponsored research involving creatine supplementation, has received creatine supplement donations for scientific studies and travel support for conference presentations involving creatine supplementation. In addition, ER serves on the Scientific Advisory Board for Alzchem (a company that manufactures creatine) and as an expert witness/consultant in legal cases involving creatine supplementation.

HR: have received research grants and supplement donations for scientific studies from AlzChem, Natural Alternatives International, DuPont, J.B.S., and NotCompany.

ASR serves as a scientific advisor for Alzchem and Create (companies which manufacturer creatine products).

TNZ: has no conflict in terms of financial or business interests related to creatine. TNZ has received grants and contracts to conduct research on dietary supplements; has served as a paid consultant for industry; has received honoraria for speaking at conferences and writing lay articles about sports nutrition ingredients; receives royalties from the sale of several dietary supplement products (but not creatine); and has served as an expert witness on behalf of the plaintiff and defense in cases involving dietary supplements. TNZ is also a co-inventor of multiple patent applications in dietary supplements, applied nutrition, and bioactive compounds.

JRS: has received grants and contracts to research dietary supplements, served as a paid consultant for industry, and received honoraria for speaking at conferences and writing lay articles about sports nutrition ingredients and topics.

MAT: is the founder and CEO of Exerkine Corporation and the company sells two products that contain creatine monohydrate. The creatine monohydrate used in the two products is from Alzchem (a company that manufactures creatine).

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