Creatine Supplementation

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Creatine is a popular ergogenic aid among athletic populations with consistent evidence indicating that creatine supplementation also continues to be commonly used among adolescent populations. In addition, the evidence base supporting the therapeutic benefits of creatine supplementation for a plethora of clinical applications in both adults and children continues to grow. Among pediatric populations, a strong rationale exists for creatine to afford therapeutic benefits pertaining to multiple neuromuscular and metabolic disorders, with preliminary evidence for other subsets of clinical populations as well. Despite the strong evidence supporting the efficacy and safety of creatine supplementation among adult populations, less is known as to whether similar physiological benefits extend to children and adolescent populations, and in particular those adolescent populations who are regularly participating in high-intensity exercise training. While limited in scope, studies involving creatine supplementation and exercise performance in adolescent athletes generally report improvements in several ergogenic outcomes with limited evidence of ergolytic properties and consistent reports indicating no adverse events associated with supplementation.

ergogenic aid dietary supplement

1. Effects of Creatine Supplementation on Creatine Content

Although limited in number, select studies have demonstrated that creatine supplementation is an effective nutritional strategy to promote increases in the phosphocreatine content and energy status of the cell among pediatric populations [1][2]; however, some evidence suggests this is potentially so, but to a lesser extent when compared to what is commonly reported in adult populations [3]. Depending on baseline levels of creatine content, which tend to be heavily influenced by exogenous creatine intake [4], increases of 10–40% in creatine or phosphocreatine content within skeletal muscle tissue are routinely reported following periods of creatine supplementation in adult populations [3]. Interestingly, preliminary evidence suggests that an age-dependent effect of creatine supplementation may exist regarding intramuscular creatine uptake, thereby indicating that the development of age-specific supplementation strategies may be warranted [1][2]. Further, research in adult populations [5][6][7] has indicated a moderate degree of variability in tissue uptake response to creatine supplementation protocols. It is currently unknown if similar variabilities (i.e., responder vs. nonresponder effects) are also present among children and adolescents. Due to age and ethical considerations, the majority of research in pediatric populations has relied on magnetic resonance imaging or laboratory markers as indirect measures of creatine and phosphocreatine content rather than through muscle biopsies, which is a common technique used for measuring intramuscular creatine content in adult populations. Additionally, lower doses of creatine are sometimes used among pediatric populations, which is also likely to influence the magnitude of changes observed in creatine

content following a supplementation period. Therefore, it is difficult to directly compare the efficacy of creatine supplementation strategies between age groups when different techniques are used to quantify creatine content and different dosing strategies may be employed. However, a study by Solis et al. [2] was able to examine changes in brain and muscle phosphocreatine content across three age groups (children, *n* = 15, adult omnivores, *n* = 17, adult vegetarians, *n* = 14, and elderly adults, *n* = 18) using ^{31}P-magnetic resonance spectroscopy, following a standard creatine loading protocol (0.3 g/kg/day for 7 days). Results indicated intramuscular phosphocreatine content significantly increased by 13.9% while brain phosphocreatine levels only increased by 2.1% among the group of children [2]. Comparatively, following the same creatine dosing regimen, larger increases in muscle phosphocreatine content were observed in the elderly (22.7%) but not adult omnivores (10.3%) when compared to the children. It is also worth noting that lower baseline levels of muscle phosphocreatine content were observed in the children compared to the adult groups. Using a lower dose (5 g/day), but over an 8-week period, Banerjee et al. [1] reported significantly greater increases in the mean phosphocreatine/inorganic phosphate ratio following creatine supplementation compared to placebo (Creatine: 4.7; 95% CI: 3.9–5.6 vs. Placebo 3.3; 95% CI 2.5–4.2; *p* = 0.03) in patients with Duchenne Muscular Dystrophy. Alternatively, contradictory reports to these outcomes regarding the efficacy of creatine supplementation have indicated little to no impact on intramuscular phosphocreatine content; however the relative dose used in these studies may have been too low (0.1 g/kg/day for 12 weeks) to elicit any meaningful changes in creatine content [6][7]. Additionally, it is also worth noting these studies were conducted in patients with childhood-onset systemic lupus erythematosus and juvenile dermatomyositis, which may have influenced the efficacy of creatine supplementation in its ability to increase phosphocreatine content. Preliminary evidence among specialized clinical populations with inborn errors of metabolism, such as creatine deficiencies, has also indicated that creatine supplementation can positively influence brain creatine content with a subsequent influence on cognition, natural development, and quality of life [8][9][10]. However, as highlighted previously by Solis et al. [2], it was reported that a standard creatine loading regimen (0.3 g/kg/day for 7 days) in prepubescent children, omnivore adults, vegetarian adults, and elderly adults was not able to elicit significant changes in brain phosphocreatine content [2]. Similar findings have also been observed in healthy young children between the ages of 10 to 12 years of age [11], which failed to observe significant increases in brain creatine content following creatine supplementation. However, a review by Dolan et al. [12] highlighted multiple studies in adult populations, all of which utilized varying creatine supplementation strategies (2–20 g per day from 5 days to 8 weeks), that were able to demonstrate significant increases in brain creatine and phosphocreatine content following supplementation. It is possible that higher doses of creatine over longer periods of time may be required for meaningful increases in brain creatine content to occur among healthy populations as has been previously suggested [12]. The potential increase in brain creatine content following supplementation may also be age-dependent. Nevertheless, more research is needed to identify the extent to which creatine supplementation can impact brain creatine levels and whether or not modified creatine supplementation strategies for this purpose are warranted.

2. Performance Benefits

When compared to adults, a limited number of controlled investigations examining the ability of creatine supplementation to impact measures of exercise performance among adolescent populations exist. All available studies to date, have been completed in only two types of athletes: swimming (n = 5) and soccer (n = 4). Additionally, studies were completed across all parts of the globe with two studies being completed in Brazil and one study being completed in Hungary, Australia, USA, United Kingdom, Iran, and Yugoslavia. The studies completed on swimmers differed somewhat in the dosing regimen that was employed. Three of the studies utilized a loading phase for the entirety of the supplementation regimen, incorporating doses of 21 g per day for nine days, 20 g per day for five days, and 20 g per day for 4 days [13][14][15]. The other two studies used a combination of a loading (5 days at 20 g/day or four days at 25 g/day) and a maintenance phase (5 g/day for 22 days or 5 g/day for 2 months) [16][17]. Various parameters of swimming performance were assessed ranging from in-water sprint swimming performance to power outputs completed during a swim bench/ergometer test. All studies that reported outcomes within the initial 4–9 days of supplementation identified an improvement in various performance measures such as swim bench test performance, sprint swimming performance, dynamic strength, and anaerobic exercise performance. The longest study by Theodorou et al. [17], reported improvements in interval swimming exercise performance after the loading phase, but no further improvement after a maintenance dose was administered. Alternatively, Dawson et al. [16] reported improvements in swim bench performance, but not sprint swimming performance after completion of both a loading and maintenance phase. While not directly performance related, Juhasz et al. [18] indicated that creatine supplementation may also be an effective strategy to support the rehabilitation of overuse-associated tendinitis in adolescent swimmers when combined with a targeted physical therapy program. Notably, when indicated by the authors, no adverse events were reported in any of these studies.

The studies that enrolled adolescent soccer athletes as study participants ranged in duration from 7–49 days. Three studies were seven days in duration and employed loading phases that each delivered different loading doses (0.03 g/kg/day, 20 g/day, and 30 g/day) [19][20][21]. One study [22] was seven weeks in duration and used a seven-day loading phase (20 g/day) followed by a six-week maintenance dose of 5 g/day. All studies were placebo-controlled. Of interest, all three studies that were <7 days in duration, reported statistically significant improvements in various performance outcomes. For example, Mohebbi et al. [19] reported a significant improvement in repeat sprinting and soccer dribbling performance, while Ostojic et al. [20] reported improvements in performance of a soccer dribbling test, countermovement jump, and power production during a sprint. Lastly, Yanez-Silva et al. [21] reported improvements in peak and mean power output as well as total work completed during a Wingate anaerobic capacity test. The remaining study, Claudino et al. [22] failed to report any improvements in lower body power production after 14 male adolescent soccer athletes completed a one-week loading and a six-week maintenance dose phase. Finally, and similar to what was observed with the studies involving swimming, creatine was well tolerated with no adverse events being reported. A summary table of these studies has been included in Table 1.

Table 1. Efficacy of creatine use in adolescents on exercise performance.

Author Year (Country)	Subjects	Design	Duration	Dosing Protocol	Primary Variables	Results	Adverse Events
				Swimming			
Dawson et al. 2002 (Australia) [16]	10 male, 10 female (16.4 ± 1.8 years) swimmers	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. 1997 (USA) [13]	18 (11 female, 7 male) 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
Juhasz et al. 2009 (Hungary) [14]	16 male fin swimmers (15.9 ± 1.6 years)	Randomized, placebo-controlled, single-blind trail	5 days	20 g/day	Average power, dynamic strength (swim based tests)	↑ anaerobic performance; ↑ dynamic strength	None reported
Theodorou et al. 1999 (UK) [17]	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. 2005 (United Kingtom) [15]	10 high performance swimmers (males: *n* = 6; females: *n* = 4) (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 CrM + Carbohydrate group only
				Soccer			
Claudino et al. 2014 (Brazil) [22]	14 male Brazilian elite soccer players (18.3 ± 0.9 years)	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. 2012	17 adolescent	Randomized, double-blind,	7 days	20 g/day	Repeated sprint test, soccer	↑ repeat sprint performance;	None reported

Author Year (Country)	Subjects	Design	Duration	Dosing Protocol	Primary Variables	Results	Adverse Events
(Iran) [19]	soccer players (17.2 ± 1.4 years)	placebo-controlled			dribbling performance and shooting accuracy	↑ dribbling performance	
Ostojic et al. 2004 (Yugoslavia) [20]	20 adolescent male soccer players (16.6 ± 1.9 years)	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
Yanez-Silva et al. 2017 (Brazil) [21]	Elite youth soccer players (17.0 ± 0.5 years)	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

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3. Clinical Applications

= 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. 2018 [28].

Over the past 30 years, the discovery of inborn errors of metabolism and the potential physiological, neurological, and neuroprotective benefits of creatine have led to advancements in the therapeutic use of creatine. As such, several pediatric clinical populations have been shown to benefit from creatine supplementation, which notably includes patients with genetic defects associated with creatine deficiency. Table 2 presents a summary of studies that have examined the therapeutic benefits of creatine supplementation for a variety of clinical disorders. To date, the majority of clinical trials investigating the therapeutic potential of creatine supplementation in pediatric populations have focused on creatine (and/or creatine transporter) deficiencies, inborn errors of metabolism, neuromuscular disorders, and myopathies [1][24][25][26][27][28][29]. Guanidinoacetate methyltransferase (GAMT) and arginine:glycine amidinotransferase (AGAT) deficiency, are types of inborn errors of creatine metabolism, collectively characterized as cerebral creatine synthesis deficiencies [27][30]. Several studies and case reports have indicated that creatine supplementation can restore tissue creatine content and improve some of the symptoms resulting from creatine deficiencies [31][32][33][34]. Since its discovery in 1994, GAMT deficiency has shown to be treatable through creatine supplementation strategies [31][33]. For example, in 1996, Stockler et al. [34] treated an infant patient with GAMT deficiency using a creatine replacement therapy of 4–8 g/day over a 25-month period and reported substantial clinical improvement, normalization of brain MRI abnormalities, and improvements in electroencephalogram readings post-treatment. Since that time, several additional case reports and reviews have been published, highlighting effective strategies to diagnose and treat cerebral creatine deficiency with consistent improvements in intellectual development reported, especially when early detection and ensuing treatment were employed [31][32]. While similar in nature, AGAT deficiency is extremely rare with only 20 documented cases worldwide [32]. AGAT deficiency is also an autosomal recessive disorder that disrupts the biosynthesis of creatine and is associated with a variety of clinical features such as intellectual development disorder, speech delays, autistics behaviors, and occasional seizures [32]. Thankfully, AGAT also appears to betreatable with creatine supplementation. For example, Ndika et al. [8] treated a 9-year-old female pediatric patient with AGAT deficiency with up to 800 mg/kg/day of creatine over an 8-year period and reported partial recovery of cerebral creatine levels

with the patient demonstrating superior nonverbal and academic abilities at age 9, compared to initially presenting with a score of 43% of her chronological age at 16 months when assessed using the Bayley's Infant Development Scale. Although similar, creatine transporter deficiency is another inborn error of metabolism that can result in creatine deficiencies in select tissues, particularly within the brain [31]. Creatine transporters are membrane-bound transport proteins that have been found in a variety of different tissues and are required for tissue uptake of creatine against its concentration gradient. Moreover, creatine transporter 1 (CrT1) is expressed ubiquitously across human tissues and deficiencies of this protein are another type of creatine metabolism disorder that can result in brain atrophy, intellectual disabilities, and developmental delays [31]. However, this defect is not as responsive to exogenous creatine supplementation strategies, as the deficiency is attributable to an inability to transport creatine across the cell membrane, rather than a lack of creatine availability [27]. As such, current research has focused on identifying alternative strategies that may enhance brain creatine content in these populations. For example, recent work has demonstrated early promise with the use of creatine fatty esters and lipid nanocapsules as a nutrition-based therapeutic treatment for creatine transporter deficiency [35][36]. These creatine esters and lipid based nanocapsules are better able to cross the blood−brain barrier, thereby helping to increase brain creatine content and correct the creatine deficiency [36].

Table 2. Efficacy of creatine in clinical settings.

Author Year	Subjects	Design	Duration	Dosing Protocol	Primary Variables	Results	Adverse Events
Sipila et al. 1981 [37]	7 (3 adolescents) patients with gyrate atrophy of retina	Open label treatment intervention	12 months	1.5 g/day	Visual acuity, muscle fiber characteristics, laboratory markers of creatine metabolism	↔ Visual acuity; ↑ Thickness of Type II muscle fibers	No side effects reported
Vannas-Sulonen et al. 1985 [38]	13 patients (9 male, 4 female) between ages of 6–31 years diagnosed with gyrate atrophy of the choroid	Prospective, open-label cohort	36–72 months	0.25–0.5 g dose 3×/day	Morphological and eye function assessments	↔ Cr supplementation did not prevent normal deterioration; ↓ Muscle atrophy, primarily in type II fibers	None reported
Walter et al. 2000 [39]	36 patients with multiple types of muscular dystrophies (overall mean age: 26 ± 16 years) 8 patients with Duchenne	Randomized, double-blind, placebo-controlled	8 weeks	10 g/day (adults) 5 g/day (children)	Muscular performance, neuromuscular symptoms score, vital capacity and qualitative assessments	↑ (3%) in muscle strength; ↑ (10%) in neurological symptoms. Children tended to experience	None reported. Indicated to be well-tolerated.

Author Year	Subjects	Design	Duration	Dosing Protocol	Primary Variables	Results	Adverse Events
	dystrophy (mean age: 10 ± 3 years)					greater strength changes.	
Braegger et al. 2003 [40]	18 cystic fibrosis patients (7 F, 11 M) ranging in age from 8–18 years	Prospective open-label pilot	Supplemented for 12 weeks; monitored for 24–36 weeks	12 g/day for 1st week; 6 g/day for remaining 11 weeks	Lung function, strength, and clinical parameters	↔ Lung function or sweat electrolytes. ↑ (18%) in peak isometric strength	One patient experienced transient muscle pain; No other side effects
Louis et al. 2003 [41]	15 boys with muscular dystrophy (mean age: 10.8 ± 2.8 years)	Double-blind, placebo-controlled, cross-over study design	3 months, with 2 months washout	3 g/day	Muscle function, densitometry, markers of hepatic and renal function, magnetic resonance spectroscopy	↑ MVC by 15% ↑ TTE (~2×) ↑ TJS ↑ LS and WB BMD in ambulatory patients ↑ NTx/creatinine ratio in ambulatory patients	No changes in liver or kidney markers
Tarnopolsky et al. 2004 [25]	30 boys with Duchenne muscular dystrophy; mean age: 10 ± 3 years; height: 129.2 ± 16.0 cm; weight: 35.3 ± 15.8 kg	Double-blind, randomized, crossover trial	4 months	0.10 g/kg/day	Pulmonary function, strength, body composition, bone health, task function, blood & urinary markers	↑ handgrip strength, fat-free mass, and bone markers ↔ functional tasks or activities of daily living	None
Escolar et al. 2005 [29]	50 ambulatory steroid naïve boys with Duchenne Muscular Dystrophy (mean age: 6 years)	Double-blind, placebo-controlled, randomized	6 months	5 g/day of creatine powder, 0.3 mg/kg of glutamine (×2 per day), or placebo	Manual muscle performance, quantitative muscle testing, time to rise	↔ primary or secondary outcomes measures	Deemed safe and well-tolerated with no side effects reported.
Sakellaris et al. 2008 [42]	39 children/adolescents following traumatic brain injury	Open-label pilot study	6 months	0.4 g/kg/day	Duration of amnesia, duration of intubation, and intensive care unit stay post	↓ Amnesia ↓ Intubation period ↓ Intensive care unit stay	None

Author Year	Subjects	Design	Duration	Dosing Protocol	Primary Variables	Results	Adverse Events
					traumatic brain injury		
Bourgeois et al. 2008 [43]	9 children with lymphoblastic leukemia during chemotherapy (in treatment group); mean age of 7.6 years, 50 healthy children as history controls	Cross sectional, mixed cohort designs	16 weeks	0.1 g/kg/day	Height, weight, BMI, BMD, BMC, FFM, %BF, serum creatinine	↑ %BF and BMI	None reported
Banerjee et al. 2010 [1]	33 ambulatory male patients with Duchenne muscular dystrophy	Randomized, placebo-controlled, single-blind trial	8 weeks	Cr, 5 g/day (n = 18)	Cellular energetics, manual muscle test score and functional status	↑ in PCr/Pi ratios	None reported
Van de Kamp et al. 2012 [10]	9 boys with creatine transporter defect	Long-term follow-up investigation	4–6 years	Cr (400 mg/kg/day) and L-arginine (400 mg/kg/day)	Locomotor and personal social IQ subscales	Initial ↑ in locomotor and personal social IQ subscales; No lasting clinical improvement was recorded	No adverse events were reported.
Hyashi et al. 2014 [7]	15 participants with childhood systemic lupus erythematosus	Double-blind, placebo controlled, cross-over design	12 weeks with 8 week washout period	0.1 g/kg/day	Muscle function, body composition, biochemical markers of bone, aerobic conditioning, quality of life	↔ intramuscular PCr, muscle function, and aerobic conditioning parameters, body composition, quality of life	↔ laboratory parameters; No side effects reported
Solis et al. 2016 [6]	Patients with juvenile dermatomyositis (mean age: 13 ± 4 years)	Randomized, double-blind, placebo-controlled, crossover trial	12 weeks	0.1 g/kg/day	Primary: muscle function Secondary: body composition, biochemical markers of bone	↔ Muscle function, intramuscular PCr content, or other secondary outcomes measures	No side efforts reported. ↔ Markers of kidney function

e in the muscle ations of creatine, phosphocreatine, and ATP in addition to subsequent neuromuscular impairments and muscle weakness [46]. As such, a strong underlying physiological rationale exists to support the potential of creatine supplementation as a therapeutic agent in the management of myopathies. For example, Duchenne's muscular dystrophy is one such myopathy that is progressive in nature with no known cure. Patients are often prescribed corticosteroids to slow disease progression, which can have several adverse side effects when used long-term. Because of the catabolic nature of corticosteroid therapy, and musculoskeletal pathology associated with muscular dystrophy, creatine supplementation has been identified as a therapeutic agent to potentially counteract the deleterious effects of both the disease, and comorbidities which arise secondary to the primary corticosteroid treatment. Favorable improvements have been observed for fat-free mass and strength in pediatric patients [25]. A major challenge with clinical trials investigating the therapeutic benefits of creatine supplementation in patients with various types of

Author Year	Subjects	Design	Duration	Dosing Protocol	Primary Variables	Results	Adverse Events
			[37][47]		remodeling, cytokines, laboratory markers of kidney function, aerobic conditioning, and quality of life		
Kalamitsou et al. 2019 [44]	22 children (9 F, 13 M) with refractory epilepsy ranging in age from 10 months to 8 years	Prospective cohort	3–12 months follow-up	0.4 g/kg/day creatine + ketogenic diet	Proportion of responders to ketogenic diet [38][47]	6/22 (27%) responded to creatine addition to ketogenic diet	None reported, well-tolerated with no exacerbations of underlying pathology [48][49]
Dover et al. 2020 [45]	13 (7 F, 6 M) patients ranging in age from 7–14 years with juvenile dermatomyositis; 25.6–64.6 kg; 14.3–22.9 kg/m^2	Randomized, double-blind, placebo-controlled [50]	6 months	Up to 40 kg was 150 mg/kg/day >40 kg was 4.69 g/m^2/day	Safety and tolerability muscle function, disease activity, aerobic capacity, muscle strength	↔ in muscle function, strength, aerobic capacity, fatigue, physical activity ↓ in muscle pH following exercise	No adverse events reported

[52][53]. Creatine supplementation has also been used as an experimental therapeutic agent for conditions pertaining to hypoxia and energy-related brain pathologies such as traumatic brain injuries or cerebral ischemia in pediatric patients [54][29][55]. There has also been recent interest in examining the potential benefits of creatine supplementation for pregnant women with potential benefits extending to the developing fetus [56][57]. Currently, clinical trials are underway to better understand how creatine may affect both the mother and developing fetus [56]. It is also worth noting that a growing body of evidence exists demonstrating that creatine may also confer a variety of physiological benefits for multiple clinical conditions in adult populations, such as mitochondrial disease, neurological disorders, and autoimmune disorders [27][55], but the extent to which these findings may extend to pediatric populations requires more research due to the limited data currently available. Lastly, and a point that is beyond the scope of this review, all of these findings may hold particular importance for any clinical population (adult or adolescent) who are vegetarians as they may be susceptible to low daily creatine intake through diet alone, as has been reported in adults [5][4][41].

↔ = Creatine supplementation resulted in no change in the target outcome; ↑ = Creatine supplementation resulted in an increase in the target outcome; ↓ = Creatine supplementation resulted in a decrease (directional) in the target outcome. BMI = body mass index; FFM = fat-free mass; %BF = body fat percentage; TJS = total joint stiffness; TTE = time to exhaustion; g/d = grams per day; g/kg/d = grams per kilogram of bodyweight per day; mg/kg/d = milligrams per kilogram of bodyweight per day; PCr = phosphocreatine. MVC = maximum voluntary contraction; NTx = N-terminal telopeptide of type I collagen; LS = lumbar spine; WB = whole body; BMD = bone mineral density; BMC = bone mineral content; Pi = inorganic phosphate.

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